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(54) Title: COMPOSITIONS ISOLATED FROM SKIN CELLS AND METHODS FOR THEIR USE

(57) Abstract: Isolated polynucleotides encoding polypeptides expressed in mammalian skin cells are provided, together with expression vectors and host cells comprising such isolated polynucleotides. Methods for the use of such polynucleotides and polypeptides are also provided.

COMPOSITIONS ISOLATED FROM SKIN CELLS AND METHODS FOR THEIR USE

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Technical Field of the Invention

This invention relates to polynucleotides, polypeptides, polypeptides expressed in skin cells, and various methods for treating a patient involving administration of a polypeptide or polynucleotide of the present invention.

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Background of the Invention

The skin is the largest organ in the body and serves as a protective cover. The loss of skin, as occurs in a badly burned person, may lead to death owing to the absence of a barrier against infection by external microbial organisms, as well as loss of body temperature and body fluids.

Skin tissue is composed of several layers. The outermost layer is the epidermis which is supported by a basement membrane and overlies the dermis. Beneath the dermis is loose connective tissue and fascia which cover muscles or bony tissue. The skin is a self-renewing tissue in that cells are constantly being formed and shed. The deepest cells of the epidermis are the basal cells, which are enriched in cells capable of replication. Such replicating cells are called progenitor or stem cells. Replicating cells in turn give rise to daughter cells called 'transit amplifying cells'. These cells undergo differentiation and maturation into keratinocytes (mature skin cells) as they move from the basal layer to the more superficial layers of the epidermis. In the process, keratinocytes become cornified and are ultimately shed from the skin surface. Other cells in the epidermis include melanocytes which synthesize melanin, the pigment responsible for protection against sunlight. The Langerhans cell also resides in the epidermis and functions as a cell which processes foreign proteins for presentation to the immune system.

The dermis contains nerves, blood and lymphatic vessels, fibrous and fatty tissue. Within the dermis are fibroblasts, macrophages and mast cells. Both the epidermis and dermis are penetrated by sweat, or sebaceous glands and hair follicles. Each strand of hair is derived from a hair follicle. When hair is plucked out, the hair re-grows from epithelial cells directed by the dermal papillae of the hair follicle.

When the skin surface is breached, for example in a wound, the stem cells proliferate and daughter keratinocytes migrate across the wound to reseal the tissues. The skin cells therefore possess genes activated in response to trauma. The products of these genes include several growth factors, such as epidermal growth factor, which mediate the proliferation of skin cells. The genes that are activated in the skin, and the protein products of such genes, may be developed as agents for the treatment of skin wounds. Additional growth factors derived from skin cells may also influence growth of other cell types. As skin cancers are a disorder of the growth of skin cells, proteins derived from skin that regulate cellular growth may be developed as agents for the treatment of skin cancers. Skin derived proteins that regulate the production of melanin may be useful as agents, which protect skin against unwanted effects of sunlight.

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Keratinocytes are known to secrete cytokines and express various cell surface proteins. Cytokines and cell surface molecules are proteins, which play an important role in the inflammatory response against infection, and also in autoimmune diseases affecting the skin. Genes and their protein products that are expressed by skin cells may thus be developed into agents for the treatment of inflammatory disorders affecting the skin.

Hair is an important part of a person's individuality. Disorders of the skin may lead to hair loss. Alopecia areata is a disease characterized by the patchy loss of hair over the scalp. Total baldness is a side effect of drug treatment for cancer. The growth and development of hair is mediated by the effects of genes expressed in skin and dermal papillae. Such genes and their protein products may be usefully developed into agents for the treatment of disorders of the hair follicle.

New treatments are required to hasten the healing of skin wounds, to prevent the loss of hair, enhance the re-growth of hair or removal of hair, and to treat autoimmune

and inflammatory skin diseases more effectively and without adverse effects. More effective treatments of skin cancers are also required. There thus remains a need in the art for the identification and isolation of genes encoding proteins expressed in the skin, for use in the development of therapeutic agents for the treatment of disorders including those associated with skin.

Summary of the Invention

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The present invention provides polypeptides and functional portions of polypeptides, which may be expressed in skin cells, together with polynucleotides encoding such polypeptides or functional portions thereof, expression vectors and host cells comprising such polynucleotides, and methods for their use.

In specific embodiments, isolated polynucleotides are provided that comprise a polynucleotide selected from the group consisting of: (a) sequences recited in SEQ ID NOS: 1-119, 198-276, 349-372, 399-405, 410-412, 416, 418-455, 464, 466-487, 510, 511 and 514-623; (b) complements of the sequences recited in SEQ ID NOS: 1-119, 198-276, 349-372, 399-405, 410-412, 416, 418-455, 464, 466-487, 510, 511 and 514-623; (c) reverse complements of the sequences recited in SEQ ID NOS: 1-119, 198-276, 349-372, 399-405, 410-412, 416, 418-455, 464, 466-487, 510, 511 and 514-623; (d) reverse sequences of the sequences recited in SEQ ID NOS: 1-119, 198-276, 349-372, 399-405, 410-412, 416, 418-455, 464, 466-487, 510, 511 and 514-623; (e) sequences having a 99% probability of being the same as a sequence of (a)-(d); and (f) sequences having at least 50%, 75%, 90% or 95% identity to a sequence of (a)-(d).

In further embodiments, the present invention provides isolated polypeptides comprising an amino acid sequence selected from the group consisting of: (a) sequences provided in SEQ ID NOS: 120-197, 275-348, 373-398, 406-409, 413-415, 417, 456-463, 465, 488-509, 512, 513 and 624-725; and (b) sequences having at least 50%, 75%, 90% or 95% identity to a sequence provided in SEQ ID NOS: 120-197, 275-348, 373-398, 406-409, 413-415, 417, 456-463, 465, 488-509, 512, 513 and 624-725, together with isolated polypucleotides encoding such polypeptides. Isolated polypeptides which

comprise at least a functional portion of a polypeptide comprising an amino acid sequence selected from the group consisting of: (a) sequences provided in SEQ ID NOS: 120-197, 275-348, 373-398, 406-409, 413-415, 417, 456-463, 465, 488-509, 512, 513 and 624-725; and (b) sequences having 50%, 75% or 90% identity to a sequence of SEQ ID NOS: 120-197, 275-348, 373-398, 406-409, 413-415, 417, 456-463, 465, 488-509, 512, 513 and 624-725, are also provided.

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In related embodiments, the present invention provides expression vectors comprising the above polynucleotides, together with host cells transformed with such vectors.

In a further aspect, the present invention provides a method of stimulating keratinocyte growth and motility, inhibiting the growth of epithelial-derived cancer cells, inhibiting angiogenesis and vascularization of tumors, or modulating the growth of blood vessels in a subject, comprising administering to the subject a composition comprising an isolated polypeptide, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: (a) sequences provided in SEQ ID NOS: 187, 196, 342, 343, 395, 397 and 398; and (b) sequences having at least 50%, 75%, 90% or 95% identity to a sequence provided in SEQ ID NOS: 187, 196, 342, 343, 395, 397 and 398.

Methods for modulating skin inflammation in a subject are also provided, the methods comprising administering to the subject a composition comprising an isolated polypeptide, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: (a) sequences provided in SEQ ID NOS: 338 and 347; and (b) sequences having at least 50%, 75%, 90% or 95% identity to a sequence provided in SEQ ID NOS: 338 and 347. In an additional aspect, the present invention provides methods for stimulating the growth of epithelial cells in a subject. Such methods comprise administering to the subject a composition comprising an isolated polypeptide including an amino acid sequence selected from the group consisting of: (a) sequences provided in SEQ ID NOS: 129 and 348; and (b) sequences having at least 50%, 75%, 90% or 95% identity to a sequence provided in SEQ ID NOS: 129 and 348.

In yet a further aspect, methods for inhibiting the binding of HIV-1 to leukocytes, for the treatment of an inflammatory disease or for the treatment of cancer in a subject are provided, the methods comprising administering to the subject a composition comprising an isolated polypeptide including an amino acid sequence selected from the group consisting of: (a) sequences provided in SEQ ID NOS: 340, 344, 345 and 346; and (b) sequences having at least 50%, 75%, 90% or 95% identity to a sequence provided in SEQ ID NOS: 340, 344, 345 and 346.

As detailed below, the isolated polynucleotides and polypeptides of the present invention may be usefully employed in the preparation of therapeutic agents for the treatment of skin disorders.

The above-mentioned and additional features of the present invention, together with the manner of obtaining them, will be best understood by reference to the following more detailed description. All references disclosed herein are incorporated herein by reference in their entirety as if each was incorporated individually.

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Brief Description of the Drawings

Fig. 1 shows the results of a Northern analysis of the distribution of huTR1 mRNA in human tissues. Key: He, Heart; Br, Brain; Pl, Placenta; Lu, Lung; Li, Liver; SM, Skeletal muscle; Ki, Kidney; Sp, Spleen; Th, Thymus; Pr, Prostate; Ov, Ovary.

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- Fig. 2 shows the results of a MAP kinase assay of muTR1a and huTR1a. MuTR1a (500ng/ml), huTR1a (100ng/ml) or LPS (3pg/ml) were added as described in the text.
- Fig. 3 shows the stimulation of growth of neonatal foreskin keratinocytes by muTR1a.

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- Fig. 4 shows the stimulation of growth of the transformed human keratinocyte cell line HaCaT by muTR1a and huTR1a.
- Fig. 5 shows the inhibition of growth of the human epidermal carcinoma cell line A431 by muTR1a and huTR1a.

Fig. 6 shows the inhibition of IL-2 induced growth of concanavalin A-stimulated

murine splenocytes by KS2a.

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Fig. 7 shows the stimulation of growth of rat intestinal epithelial cells (IEC-18) by a combination of KS3a plus apo-transferrin.

Fig. 8 illustrates the oxidative burst effect of TR-1 (100 ng/ml), muKS1 (100 ng/ml), SDF1α (100 ng/ml), and fMLP (10 μM) on human PBMC.

Figure 9 shows the chemotactic effect of muKS1 and SDF-1α on THP-1 cells.

Figure 10 shows the induction of cellular infiltrate in C3H/HeJ mice after intraperitoneal injections with muKS1 (50 µg), GV14B (50 µg) and PBS.

Figure 11 demonstrates the induction of phosphorylation of ERK1 and ERK2 in CV1/EBNA and HeLa cell lines by huTR1a.

Figure 12 shows the huTR1 mRNA expression in HeLa cells after stimulation by muTR1, huTGFα and PBS (100 ng/ml each).

Figure 13 shows activation of the SRE by muTR1a in PC-12 (Fig. 13A) and HaCaT (Fig. 13B) cells.

Figure 14 shows the inhibition of huTR1a mediated growth on HaCaT cells by an antibody to the EGF receptor.

Figure 15A shows the nucleotide sequence of KS1 cDNA (SEQ ID NO: 464) along with the deduced amino acid sequence (SEQ ID NO: 465) using single letter code. The 5' UTR is indicated by negative numbers. The underlined NH₂-terminal amino acids represent the predicted leader sequence and the stop codon is denoted by ***. The polyadenylation signal is marked by a double underline. Figure 15B shows a comparison of the complete open reading frame of KS1 (referred to in Fig. 15B as KLF-1) with its human homologue BRAK and with the mouse α-chemokines mCrg-2, mMig, mSDF-1, mBLC, mMIP2, mKC and mLIX. An additional five residues are present in KS1 and BRAK between cysteine 3 and cysteine 4 that have not previously been described for chemokines.

Detailed Description of the Invention

In one aspect, the present invention provides polynucleotides that were isolated from mammalian skin cells. As used herein, the term "polynucleotide" means a single or

double-stranded polymer of deoxyribonucleotide or ribonucleotide bases and includes DNA and RNA molecules, both sense and anti-sense strands. The term comprehends cDNA, genomic DNA, recombinant DNA and wholly or partially synthesized nucleic acid molecules. A polynucleotide may consist of an entire gene, or a portion thereof. A gene is a DNA sequence that codes for a functional protein or RNA molecule. Operable anti-sense polynucleotides may comprise a fragment of the corresponding polynucleotide, and the definition of "polynucleotide" therefore includes all operable anti-sense fragments. Anti-sense polynucleotides and techniques involving anti-sense polynucleotides are well known in the art and are described, for example, in Robinson-Benion et al., "Anti-sense Techniques," *Methods in Enzymol.* 254(23):363-375, 1995; and Kawasaki et al., *Artific. Organs* 20(8):836-848, 1996.

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Identification of genomic DNA and heterologous species DNAs can be accomplished by standard DNA/DNA hybridization techniques, under appropriately stringent conditions, using all or part of a cDNA sequence as a probe to screen an appropriate library. Alternatively, PCR techniques using oligonucleotide primers that are designed based on known genomic DNA, cDNA and protein sequences can be used to amplify and identify genomic and cDNA sequences. Synthetic DNAs corresponding to the identified sequences and variants may be produced by conventional synthesis methods. All the polynucleotides provided by the present invention are isolated and purified, as those terms are commonly used in the art.

In specific embodiments, the polynucleotides of the present invention comprise a sequence selected from the group consisting of sequences provided in SEQ ID NOS: 1-119, 198-274, 349-372, 399-405, 410-412, 416, 418-455, 464, 466-487, 510, 511 and 514-623, and variants of the sequences of SEQ ID NOS: 1-119, 198-274, 349-372, 399-405, 410-412, 416, 418-455, 464, 466-487, 510, 511 and 514-623. Polynucleotides that comprise complements of such sequences, reverse complements of such sequences, or reverse sequences of such sequences, together with variants of such sequences, are also provided.

The definition of the terms "complement," "reverse complement," and "reverse sequence," as used herein, is best illustrated by the following example. For the sequence 5' AGGACC 3', the complement, reverse complement, and reverse sequence are as follows:

complement 3' TCCTGG 5'

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reverse complement 3' GGTCCT 5'

reverse sequence 5' CCAGGA 3'.

As used herein, the term "complement" refers to sequences that are fully complementary to a sequence disclosed herein.

In another aspect, the present invention provides isolated polypeptides and functional portions of polypeptides encoded, or partially encoded, by the above polynucleotides. As used herein, the term "polypeptide" encompasses amino acid chains of any length, including full length proteins, wherein the amino acid residues are linked by covalent peptide bonds. The term "polypeptide encoded by a polynucleotide" as used herein, includes polypeptides encoded by a polynucleotide which comprises a partial isolated DNA sequence provided herein. In specific embodiments, the inventive polypeptides comprise an amino acid sequence selected from the group consisting of sequences provided in SEQ ID NOS: 120-197, 275-348, 373-398, 406-409, 413-415, 417, 456-463, 465, 488-509, 512, 513 and 624-725, as well as variants of such sequences.

Polypeptides of the present invention may be produced recombinantly by inserting a DNA sequence that encodes the polypeptide into an expression vector and expressing the polypeptide in an appropriate host. Any of a variety of expression vectors known to those of ordinary skill in the art may be employed. Expression may be achieved in any appropriate host cell that has been transformed or transfected with an expression vector containing a DNA molecule that encodes a recombinant polypeptide. Suitable host cells include prokaryotes, yeast, and higher eukaryotic cells. Preferably, the host cells employed are *E. coli*, insect, yeast, or a mammalian cell line such as COS or CHO. The DNA sequences expressed in this manner may encode naturally occurring polypeptides, portions of naturally occurring polypeptides, or other variants thereof.

In a related aspect, polypeptides are provided that comprise at least a functional portion of a polypeptide having an amino acid sequence selected from the group consisting of sequences provided in SEQ ID NOS: 120-197, 275-348, 373-398, 406-409, 413-415, 417, 456-463, 465, 488-509, 512-513 and 624-725, and variants thereof. As used herein, the "functional portion" of a polypeptide is that portion which contains the active site essential for affecting the function of the polypeptide, for example, the portion of the molecule that is capable of binding one or more reactants. The active site may be made up of separate portions present on one or more polypeptide chains and will generally exhibit high binding affinity.

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Functional portions of a polypeptide may be identified by first preparing fragments of the polypeptide by either chemical or enzymatic digestion of the polypeptide, or by mutation analysis of the polynucleotide that encodes the polypeptide and subsequent expression of the resulting mutant polypeptides. The polypeptide fragments or mutant polypeptides are then tested to determine which portions retain biological activity, using, for example, the representative assays provided below.

Portions and other variants of the inventive polypeptides may also be generated by synthetic or recombinant means. Synthetic polypeptides having fewer than about 100 amino acids, and generally fewer than about 50 amino acids, may be generated using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. See Merrifield, J. Am. Chem. Soc. 85:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/Applied BioSystems, Inc. (Foster City, California), and may be operated according to the manufacturer's instructions. Variants of a native polypeptide may be prepared using standard mutagenesis techniques, such as oligonucleotide-directed site-specific mutagenesis (Kunkel, T., Proc. Natl. Acad. Sci. USA 82:488-492, 1985). Sections of DNA sequence

may also be removed using standard techniques to permit preparation of truncated polypeptides.

In general, the polypeptides disclosed herein are prepared in an isolated, substantially pure, form. Preferably, the polypeptides are at least about 80% pure, more preferably at least about 90% pure, and most preferably at least about 99% pure. In certain preferred embodiments, described in detail below, the isolated polypeptides are incorporated into pharmaceutical compositions or vaccines for use in the treatment of skin disorders.

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As used herein, the term "variant" comprehends nucleotide or amino acid sequences different from the specifically identified sequences, wherein one or more nucleotides or amino acid residues is deleted, substituted, or added. Variants may be naturally occurring allelic variants, or non-naturally occurring variants. In certain preferred embodiments, variants of the inventive sequences retain certain, or all, of the functional characteristics of the inventive sequence. Variant sequences (polynucleotide or polypeptide) preferably exhibit at least 50%, more preferably at least 75%, and most preferably at least 90% or 95% identity to a sequence of the present invention. The percentage identity is determined by aligning the two sequences to be compared as described below, determining the number of identical residues in the aligned portion, dividing that number by the total number of residues in the inventive (queried) sequence, and multiplying the result by 100.

Polynucleotide or polypeptide sequences may be aligned, and percentages of identical nucleotides in a specified region may be determined against another polynucleotide or polypeptide, using computer algorithms that are publicly available. Two exemplary algorithms for aligning and identifying the similarity of polynucleotide sequences are the BLASTN and FASTA algorithms. The alignment and similarity of polypeptide sequences may be examined using the BLASTP and algorithm. BLASTX and FASTX algorithms compare nucleotide query sequences translated in all reading frames against polypeptide sequences. The BLASTN, BLASTP and BLASTX algorithms are available on the NCBI anonymous FTP server (ftp://ncbi.nlm.nih.gov)

under /blast/executables/ and are available from the National Center for Biotechnology Information (NCBI), National Library of Medicine, Building 38A, Room 8N805, Bethesda, MD 20894 USA.

The FASTA and FASTX algorithms are available on the Internet at the ftp site ftp://ftp.Virginia.edu/pub/. The FASTA software package is also available from the University of Virginia by contacting David Hudson, Assistant Provost for Research, University of Virginia, PO Box 9025, Charlottesville, VA 22906-9025. The FASTA algorithm, set to the default parameters described in the documentation and distributed with the algorithm, may be used in the determination of polynucleotide variants. The readme files for FASTA and FASTX v1.0x that are distributed with the algorithms describe the use of the algorithms and describe the default parameters. The use of the FASTA and FASTX algorithms is also described in Pearson, and Lipman, *Proc. Natl. Acad. Sci. USA* 85:2444-2448, 1988; and Pearson, *Methods in Enzymol.* 183:63-98, 1990.

The BLASTN algorithm version 2.0.4 [Feb-24-1998], 2.0.6 [Sept-16-1998] and 2.0.11 [Jan-20-2000], set to the default parameters described in the documentation and distributed with the algorithm, is preferred for use in the determination of polynucleotide variants according to the present invention. The BLASTP algorithm version 2.0.4, 2.0.6 and 2.0.11, set to the default parameters described in the documentation and distributed with the algorithm, is preferred for use in the determination of polypeptide variants according to the present invention. The use of the BLAST family of algorithms, including BLASTN, BLASTP and BLASTX is described in the publication of Altschul, et al., Nucleic Acids Res. 25:3389-3402, 1997.

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The following running parameters are preferred for determination of alignments and similarities using BLASTN that contribute to the E values and percentage identity for polynucleotides: Unix running command with default parameters thus: blastall -p blastn -d embldb -e 10 -G 0 -E 0 -r 1 -v 30 -b 30 -i queryseq -o results; and parameters are: -p Program Name [String]; -d Database [String]; -e Expectation value (E) [Real]; -G Cost to open a gap (zero invokes default behavior) [Integer]; -E Cost to extend a gap (zero

invokes default behavior) [Integer]; -r Reward for a nucleotide match (blastn only) [Integer]; -v Number of one-line descriptions (V) [Integer]; -b Number of alignments to show (B) [Integer]; -i Query File [File In]; -o BLAST report Output File [File Out] Optional. The following running parameters are preferred for determination of alignments and similarities using BLASTP that contribute to the E values and percentage identity for polypeptides: blastall -p blastp -d swissprotdb -e 10 -G 1 -E 11 -r 1 -v 30 -b 30 -i queryseq -o results; and the parameters are: -p Program Name [String]; -d Database [String]; -e Expectation value (E) [Real]; -G Cost to open a gap (zero invokes default behavior) [Integer]; -E Cost to extend a gap (zero invokes default behavior) [Integer]; -v Number of one-line descriptions (v) [Integer]; -b Number of alignments to show (b) [Integer]; -I Query File [File In]; -o BLAST report Output File [File Out] Optional.

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The "hits" to one or more database sequences by a queried sequence produced by BLASTN, BLASTP, FASTA, or a similar algorithm, align and identify similar portions of sequences. The hits are arranged in order of the degree of similarity and the length of sequence overlap. Hits to a database sequence generally represent an overlap over only a fraction of the sequence length of the queried sequence.

As noted above, the percentage identity of a polynucleotide or polypeptide sequence is determined by aligning polynucleotide and polypeptide sequences using appropriate algorithms, such as BLASTN or BLASTP, respectively, set to default parameters; identifying the number of identical nucleic or amino acids over the aligned portions; dividing the number of identical nucleic or amino acids by the total number of nucleic or amino acids of the polynucleotide or polypeptide of the present invention; and then multiplying by 100 to determine the percentage identity. By way of example, a queried polynucleotide having 220 nucleic acids has a hit to a polynucleotide sequence in the EMBL database having 520 nucleic acids over a stretch of 23 nucleotides in the alignment produced by the BLASTN algorithm using the default parameters. The 23 nucleotide hit includes 21 identical nucleotides, one gap and one different nucleotide. The percentage identity of the queried polynucleotide to the hit in the EMBL database is

thus 21/220 times 100, or 9.5%. The identity of polypeptide sequences may be determined in a similar fashion.

The BLASTN and BLASTX algorithms also produce "Expect" values for polynucleotide and polypeptide alignments. The Expect value (E) indicates the number of hits one can "expect" to see over a certain number of contiguous sequences by chance when searching a database of a certain size. The Expect value is used as a significance threshold for determining whether the hit to a database indicates true similarity. For example, an E value of 0.1 assigned to a polynucleotide hit is interpreted as meaning that in a database of the size of the EMBL database, one might expect to see 0.1 matches over the aligned portion of the sequence with a similar score simply by chance. By this criterion, the aligned and matched portions of the sequences then have a probability of 90% of being the same. For sequences having an E value of 0.01 or less over aligned and matched portions, the probability of finding a match by chance in the EMBL database is 1% or less using the BLASTN algorithm. E values for polypeptide sequences may be determined in a similar fashion using various polypeptide databases, such as the SwissProt database.

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According to one embodiment, "variant" polynucleotides and polypeptides, with reference to each of the polynucleotides and polypeptides of the present invention, preferably comprise sequences having the same number or fewer nucleic or amino acids than each of the polynucleotides or polypeptides of the present invention and producing an E value of 0.01 or less when compared to the polynucleotide or polypeptide of the present invention. That is, a variant polynucleotide or polypeptide is any sequence that has at least a 99% probability of being the same as the polynucleotide or polypeptide of the present invention, measured as having an E value of 0.01 or less using the BLASTN or BLASTX algorithms set at the default parameters. According to a preferred embodiment, a variant polynucleotide is a sequence having the same number or fewer nucleic acids than a polynucleotide of the present invention that has at least a 99% probability of being the same as the polynucleotide of the present invention, measured as having an E value of 0.01 or less using the BLASTN algorithm set at the default

parameters. Similarly, according to a preferred embodiment, a variant polypeptide is a sequence having the same number or fewer amino acids than a polypeptide of the present invention that has at least a 99% probability of being the same as the polypeptide of the present invention, measured as having an E value of 0.01 or less using the BLASTP algorithm set at the default parameters.

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Variant polynucleotide sequences will generally hybridize to the recited polynucleotide sequences under stringent conditions. As used herein, "stringent conditions" refers to prewashing in a solution of 6X SSC, 0.2% SDS; hybridizing at 65°C, 6X SSC, 0.2% SDS overnight; followed by two washes of 30 minutes each in 1X SSC, 0.1% SDS at 65 °C and two washes of 30 minutes each in 0.2X SSC, 0.1% SDS at 65 °C.

As used herein, the term "x-mer," with reference to a specific value of "x," refers to a polynucleotide or polypeptide, respectively, comprising at least a specified number ("x") of contiguous residues of: any of the polynucleotides provided in SEQ ID NO: 1-119, 198-274, 349-372, 399-405, 410-412, 416, 418-455, 464, 466-487, 510, 511 and 514-623; or any of the polypeptides set out in SEQ ID NO: 120-197, 275-348, 373-398, 406-409, 413-415, 417, 456-463, 465, 488-509, 512, 513 and 624-725. The value of x may be from about 20 to about 600, depending upon the specific sequence.

Polynucleotides of the present invention comprehend polynucleotides comprising at least a specified number of contiguous residues (x-mers) of any of the polynucleotides identified as SEQ ID NO: 1-119, 198-274, 349-372, 399-405, 410-412, 416, 418-455, 464, 466-487, 510, 511 and 514-623, or their variants. Polypeptides of the present invention comprehend polypeptides comprising at least a specified number of contiguous residues (x-mers) of any of the polypeptides identified as SEQ ID NO: 120-197, 275-348, 373-398, 406-409, 413-415, 417, 456-463, 465, 488-509, 512, 513 and 624-725. According to preferred embodiments, the value of x is at least 20, more preferably at least 40, more preferably yet at least 60, and most preferably at least 80. Thus, polynucleotides of the present invention include polynucleotides comprising a 20-mer, a 40-mer, a 60-mer, an 80-mer, a 100-mer, a 120-mer, a 150-mer, a 180-mer, a 220-mer, a

250-mer; or a 300-mer, 400-mer, 500-mer or 600-mer of a polynucleotide provided in SEQ ID NOS: 1-119, 198-274, 349-372, 399-405, 410-412, 416, 418-455, 464, 466-487, 510, 511 and 514-623, or of a variant of one of the polynucleotides provided in SEQ ID NO: 1-119, 198-274, 349-372, 399-405, 410-412, 416, 418-455, 464, 466-487, 510, 511 and 514-623. Polypeptides of the present invention include polypeptides comprising a 20-mer, a 40-mer, a 60-mer, an 80-mer, a 100-mer, a 120-mer, a 150-mer, a 180-mer, a 220-mer, a 250-mer; or a 300-mer, 400-mer, 500-mer or 600-mer of a polypeptide provided in SEQ ID NOS: 120-197, 275-348, 373-398, 406-409, 413-415, 417, 456-463, 465, 488-509, 512, 513 and 624-725, or of a variant of one of the polypeptides provided in SEQ ID NOS: 120-197, 275-348, 373-398, 406-409, 413-415, 417, 456-463, 465, 488-509, 512, 513 and 624-725.

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The inventive polynucleotides may be isolated by high throughput sequencing of cDNA libraries prepared from mammalian skin cells as described below in Example 1. Alternatively, oligonucleotide probes based on the sequences provided in SEQ ID NOS: 1-119, 198-274, 349-372, 399-405, 410-412, 416, 418-455, 464, 466-487, 510, 511 and 514-623 can be synthesized and used to identify positive clones in either cDNA or genomic DNA libraries from mammalian skin cells by means of hybridization or polymerase chain reaction (PCR) techniques. Probes can be shorter than the sequences provided herein but should be at least about 10, preferably at least about 15 and most preferably at least about 20 nucleotides in length. Hybridization and PCR techniques suitable for use with such oligonucleotide probes are well known in the art (see, for example, Mullis, et al., Cold Spring Harbor Symp. Quant. Biol., 51:263, 1987; Erlieh, ed., PCR Technology, Stockton Press: NY, 1989; (Sambrook, J, Fritsch, EF and Maniatis, T, eds., Molecular Cloning: A Laboratory Manual, 2nd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor: New York, 1989). Positive clones may be analyzed by restriction enzyme digestion, DNA sequencing or the like.

In addition, DNA sequences of the present invention may be generated by synthetic means using techniques well known in the art. Equipment for automated synthesis of oligonucleotides is commercially available from suppliers such as Perkin

Elmer/Applied Biosystems Division (Foster City, California) and may be operated according to the manufacturer's instructions.

Since the polynucleotide sequences of the present invention have been derived from skin, they likely encode proteins that have important roles in growth and development of skin, and in responses of skin to tissue injury and inflammation as well as disease states. Some of the polynucleotides contain sequences that code for signal sequences, or transmembrane domains, which identify the protein products as secreted molecules or receptors. Such protein products are likely to be growth factors, cytokines, or their cognate receptors. Several of the polypeptide sequences have more than 25% similarity to known biologically important proteins and thus are likely to represent proteins having similar biological functions.

In particular, the inventive polypeptides have important roles in processes such as: induction of hair growth; differentiation of skin stem cells into specialized cell types; cell migration; cell proliferation and cell-cell interaction. The polypeptides are important in the maintenance of tissue integrity, and thus are important in processes such as wound healing. Some of the disclosed polypeptides act as modulators of immune responses, especially since immune cells are known to infiltrate skin during tissue insult causing growth and differentiation of skin cells. In addition, many polypeptides are immunologically active, making them important therapeutic targets in a whole range of disease states not only within skin, but also in other tissues of the body. Antibodies to the polypeptides of the present invention and small molecule inhibitors related to the polypeptides of the present invention may also be used for modulating immune responses and for treatment of diseases according to the present invention.

In one aspect, the present invention provides methods for using one or more of the inventive polypeptides or polynucleotides to treat disorders in a patient. As used herein, a "patient" refers to any warm-blooded animal, preferably a human.

In this aspect, the polypeptide or polynucleotide is generally present within a pharmaceutical or immunogenic composition. Pharmaceutical compositions may comprise one or more polypeptides, each of which may contain one or more of the above

sequences (or variants thereof), and a physiologically acceptable carrier. Immunogenic compositions may comprise one or more of the above polypeptides and a non-specific immune response amplifier, such as an adjuvant or a liposome, into which the polypeptide is incorporated.

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Alternatively, a pharmaceutical or immunogenic composition of the present invention may contain DNA encoding one or more polypeptides as described above, such that the polypeptide is generated in situ. In such compositions, the DNA may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid expression systems, and bacterial and viral expression systems. Appropriate nucleic acid expression systems contain the necessary DNA sequences for expression in the patient (such as a suitable promoter and terminator signal). Bacterial delivery systems involve the administration of a bacterium (such as Bacillus-Calmette-Guerin) that expresses an immunogenic portion of the polypeptide on its cell surface. In a preferred embodiment, the DNA may be introduced using a viral expression system (e.g., vaccinia or other poxvirus, retrovirus, or adenovirus), which may involve the use of a non-pathogenic, or defective, replication competent virus. Techniques for incorporating DNA into such expression systems are well known in the art. The DNA may also be "naked," as described, for example, in Ulmer et al., Science 259:1745-1749, 1993 and reviewed by Cohen, Science 259:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable beads, which are efficiently transported into the cells.

Routes and frequency of administration, as well as dosage, vary from individual to individual. In general, the pharmaceutical and immunogenic compositions may be administered by injection (e.g., intradermal, intramuscular, intravenous, or subcutaneous), intranasally (e.g., by aspiration) or orally. In general, the amount of polypeptide present in a dose (or produced in situ by the DNA in a dose) ranges from about 1 pg to about 100 mg per kg of host, typically from about 10 pg to about 1 mg per kg of host, and preferably from about 100 pg to about 1 µg per kg of host. Suitable dose

sizes will vary with the size of the patient, but will typically range from about 0.1 ml to about 5 ml.

While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of carrier will vary depending on the mode of administration. For parenteral administration, such as subcutaneous injection, the carrier preferably comprises water, saline, alcohol, a lipid, a wax, or a buffer. For oral administration, any of the above carriers or a solid carrier, such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, sucrose, and magnesium carbonate, may be employed. Biodegradable microspheres (e.g., polylactic galactide) may also be employed as carriers for the pharmaceutical compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268 and 5,075,109.

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Any of a variety of adjuvants may be employed in the immunogenic compositions of the invention to non-specifically enhance the immune response. Most adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a non-specific stimulator of immune responses, such as lipid A, Bordetella pertussis, or Mycobacterium tuberculosis. Suitable adjuvants are commercially available as, for example, Freund's Incomplete Adjuvant and Freund's Complete Adjuvant (Difco Laboratories, Detroit, Michigan), and Merck Adjuvant 65 (Merck and Company, Inc., Rahway, New Jersey). Other suitable adjuvants include alum, biodegradable microspheres, monophosphoryl lipid A, and Quil A.

The polynucleotides of the present invention may also be used as markers for tissue, as chromosome markers or tags, in the identification of genetic disorders, and for the design of oligonucleotides for examination of expression patterns using techniques well known in the art, such as the microarray technology available from Affymetrix (Santa Clara, CA). Partial polynucleotide sequences disclosed herein may be employed to obtain full length genes by, for example, screening of DNA expression libraries using hybridization probes or PCR primers based on the inventive sequences.

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The polypeptides provided by the present invention may additionally be used in assays to determine biological activity, to raise antibodies, to isolate corresponding ligands or receptors, in assays to quantitatively determine levels of protein or cognate corresponding ligand or receptor, as anti-inflammatory agents, and in compositions for skin, connective tissue and/or nerve tissue growth or regeneration. The present invention further provides methods for modulating expression of the inventive polypeptides, for example by inhibiting translation of the relevant polynucleotide. Translation of the relevant polynucleotide may be inhibited, for example, by introducing anti-sense expression vectors; by introducing antisense oligodeoxyribonucleotides or antisense phosphorothioate oligodeoxyribonucleotides; by introducing antisense oligoribonucleotides or antisense phosphorothioate oligoribonucleotides; or by other means which are well known in the art. Cell permeation and activity of antisense oligonucleotides can be enhanced by appropriate chemical modifications, such as the use of phenoxazine-substituted C-5 propynyl uracil oligonucleotides (Flanagan et al., (1999) Nat. Biotechnol. 17 (1): 48-52) or 2'-O-(2-methoxy) ethyl (2'-MOE)-oligonucleotides (Zhang et al., (2000) Nat. Biotechnol. 18: 862-867). The use of techniques involving antisense polynucleotides is well known in the art and is described, for example, in Robinson-Benion et al. (1995), Antisense techniques, Methods in Enzymol. 254 (23): 363-375 and Kawasaki et al. (1996), Artific. Organs 20 (8): 836-848.

The following Examples are offered by way of illustration and not by way of limitation.

Example 1

ISOLATION OF CDNA SEQUENCES FROM SKIN CELL EXPRESSION LIBRARIES

The cDNA sequences of the present invention were obtained by high-throughput sequencing of cDNA expression libraries constructed from specialized rodent or human skin cells as shown in Table 1.

Table 1

| | Library | Skin cell type | Source |
|----|---------|----------------|--------|
| 30 | DEPA | dermal papilla | rat |

| SKTC | keratinocytes | human |
|-------|-------------------------------|-------|
| HNFF | neonatal foreskin fibroblast | human |
| MEMS | embryonic skin | mouse |
| KSČL | keratinocyte stem cell | mouse |
| TRAM | transit amplifying cells | mouse |
| MFSE | epidermis | mouse |
| ·HLEA | small epithelial airway cells | human |
| HLEB | small epithelial airway cells | human |
| HNKA | NK cells | human |

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These cDNA libraries were prepared as described below.

cDNA Library from Dermal Papilla (DEPA)

Dermal papilla cells from rat hair vibrissae (whiskers) were grown in culture and the total RNA extracted from these cells using established protocols. Total RNA, isolated using TRIzol Reagent (BRL Life Technologies, Gaithersburg, Maryland), was used to obtain mRNA using a Poly(A) Quik mRNA isolation kit (Stratagene, La Jolla, California), according to the manufacturer's specifications. A cDNA expression library was then prepared from the mRNA by reverse transcriptase synthesis using a Lambda ZAP cDNA library synthesis kit (Stratagene).

cDNA Library from Keratinocytes (SKTC)

Keratinocytes obtained from human neonatal foreskins (Mitra, R and Nikoloff, B in *Handbook of Keratinocyte Methods*, pp. 17-24, 1994) were grown in serum-free KSFM (BRL Life Technologies) and harvested along with differentiated cells (10⁸ cells). Keratinocytes were allowed to differentiate by addition of fetal calf serum at a final concentration of 10% to the culture medium and cells were harvested after 48 hours. Total RNA was isolated from the two cell populations using TRIzol Reagent (BRL Life Technologies) and used to obtain mRNA using a Poly(A) Quik mRNA isolation kit

(Stratagene). cDNAs expressed in differentiated keratinocytes were enriched by using a PCR-Select cDNA Subtraction Kit (Clontech, Palo Alto, California). Briefly, mRNA was obtained from either undifferentiated keratinocytes ("driver mRNA") or differentiated keratinocytes ("tester mRNA") and used to synthesize cDNA. The two populations of cDNA were separately digested with *RsaI* to obtain shorter, blunt-ended molecules. Two tester populations were created by ligating different adaptors at the cDNA ends and two successive rounds of hybridization were performed with an excess of driver cDNA. The adaptors allowed for PCR amplification of only the differentially expressed sequences which were then ligated into T-tailed pBluescript (Hadjeb, N and Berkowitz, GA, *BioTechniques* 20:20-22 1996), allowing for a blue/white selection of cells containing vector with inserts. White cells were isolated and used to obtain plasmid DNA for sequencing.

cDNA library from human neonatal fibroblasts (HNFF)

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Human neonatal fibroblast cells were grown in culture from explants of human neonatal foreskin and the total RNA extracted from these cells using established protocols. Total RNA, isolated using TRIzol Reagent (BRL Life Technologies, Gaithersburg, Maryland), was used to obtain mRNA using a Poly(A) Quik mRNA isolation kit (Stratagene, La Jolla, California), according to the manufacturer's specifications. A cDNA expression library was then prepared from the mRNA by reverse transcriptase synthesis using a Lambda ZAP cDNA library synthesis kit (Stratagene).

cDNA library from mouse embryonic skin (MEMS)

Embryonic skin was micro-dissected from day 13 post coitum Balb/c mice. Embryonic skin was washed in phosphate buffered saline and mRNA directly isolated from the tissue using the Quick Prep Micro mRNA purification kit (Pharmacia, Sweden). The mRNA was then used to prepare cDNA libraries as described above for the DEPA library.

cDNA library from mouse stem cells (KSCL) and transit amplifying (TRAM) cells

Pelts obtained from 1-2 day post-partum neonatal Balb/c mice were washed and incubated in trypsin (BRL Life Technologies) to separate the epidermis from the dermis. Epidermal tissue was disrupted to disperse cells, which were then resuspended in growth medium and centrifuged over Percoll density gradients prepared according to the manufacturer's protocol (Pharmacia, Sweden). Pelleted cells were labeled using Rhodamine 123 (Bertoncello I, Hodgson GS and Bradley TR, Exp Hematol. 13:999-1006, 1985), and analyzed by flow cytometry (Epics Elite Coulter Cytometry, Hialeah, Florida). Single cell suspensions of rhodamine-labeled murine keratinocytes were then labeled with a cross reactive anti-rat CD29 biotin monoclonal antibody (Pharmingen, San Diego, California; clone Ha2/5). Cells were washed and incubated with anti-mouse CD45 phycoerythrin conjugated monoclonal antibody (Pharmingen; clone 30F11.1, 10ug/ml) followed by labeling with streptavidin spectral red (Southern Biotechnology, Birmingham, Alabama). Sort gates were defined using listmode data to identify four populations: CD29 bright rhodamine dull CD45 negative cells; CD29 bright rhodamine bright CD45 negative cells; CD29 dull rhodamine bright CD45 negative cells; and CD29 dull rhodamine dull CD45 negative cells. Cells were sorted, pelleted and snap frozen prior to storage at -80°C. This protocol was followed multiple times to obtain sufficient cell numbers of each population to prepare cDNA libraries. Skin stem cells and transit amplifying cells are known to express CD29, the integrin β1 chain. CD45, a leukocyte specific antigen, was used as a marker for cells to be excluded in the isolation of skin stem cells and transit amplifying cells. Keratinocyte stem cells expel the rhodamine dye more efficiently than transit amplifying cells. The CD29 bright, rhodamine dull, CD45 negative population (putative keratinocyte stem cells; referred to as KSCL), and the CD29 bright, rhodamine bright, CD45 negative population (keratinocyte transit amplifying cells; referred to as TRAM) were sorted and mRNA was directly isolated from each cell population using the Quick Prep Micro mRNA purification kit (Pharmacia, Sweden). The mRNA was then used to prepare cDNA libraries as described above for the DEPA library.

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cDNA Library from Epithelial Cells (MFSE)

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Skin epidermis was removed from flaky skin fsn -/- mice (The Jackson Laboratory, Bar Harbour, ME), the cells dissociated and the resulting single cell suspension placed in culture. After four passages, the cells were harvested. Total RNA, isolated using TRIzol Reagent (BRL Life Technologies, Gaithersburg, MD), was used to obtain mRNA using a Poly(A)Quik mRNA isolation kit (Stratagene, La Jolla, CA), according to the manufacturer's specifications. A cDNA expression library (referred to as the MFSE library) was then prepared from the mRNA by Reverse Transcriptase synthesis using a Lambda ZAP Express cDNA library synthesis kit (Stratagene, La Jolla, CA).

cDNA Libraries from Human Small Airway Epithelial Cells (HLEA and HLEB)

Human small airway epithelium cells SAEC (Cell line number CC-2547, Clonetics Normal Human Cell Systems, Cambrex Corporation, East Rutherford NJ) transformed with human papilloma virus E6E7 that was infected with the bacterium *Yersinia enterocolitica* (ATCC No. 51871, American Type Culture Collection, Manassas VA) and the long form of the Respiratory Syncytial Virus (RSV, ATCC No. VR26), were used as source of RNA to construct the libraries called HLEA and HLEB. Cells from the twelfth passage of SAEC cells were infected with *Y. enterocolitica* for 2 hours at an initial seed of 12.5 bacteria per cell. The cells were disinfected with gentamycin (100 μ g/ml) for 2 hours and harvested 4 hours after infection. The cells were then infected with RSV at a moiety of infection of 0.7 for 1 hour and incubated for 6 and 24 hours. Cells were harvested and the RNA extracted following standard protocols.

Total RNA, isolated using TRIzol Reagent (BRL Life Technologies, Gaithersburg, Maryland), was used to obtain mRNA using a Poly(A) Quik mRNA isolation kit (Stratagene, La Jolla, CA), according to the manufacturer's specifications. Two cDNA expression libraries were then prepared from the mRNA by reverse transcriptase synthesis using a Lambda ZAP cDNA library synthesis kit (Stratagene).

cDNA Library from Epithelial Cells (HNKA)

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The subtracted cDNA library (HNKA) from human natural killer (NK) cells was constructed as follows. A NK library was first constructed using pooled RNA extracted from primary NK cells from multiple donors, stimulated for 4 or 20 hours with IL-2 (10 ng/ml), IL-12 (1 ng/ml), IL-15 (50 ng/ml), interferon alpha (IFN-α; 1,000 U/ml) immobilized anti-CD16 or immobilized anti-NAIL antibody, or from unstimulated cells. RNA was extracted following standard procedures. cDNA was prepared using a TimeSaver kit (Pharmacia, Uppsala, Sweden) following the manufacturer's protocol. The cDNA was ligated to *Bgl*II adaptors and size-selected using cDNA sizing columns (Gibco BRL, Gaithersburg MD). The size-selected NK cDNA was ligated into a pDc 409 vector and transformed into *E. coli* DH105 cells. Single-stranded DNA was prepared from the plasmid library using a helper phage (Stratagene)

A second cDNA library (referred to as FF cDNA library) was constructed using fetal foreskin tissue. RNA was extracted and cDNA prepared following standard protocols. The cDNA was ligated into the plasmid pBluescript following standard protocols. 10 μ g of the FF cDNA library was linearized with the restriction endonuclease *Not*I and used as template to synthesize biotin-labeled cRNA using SP6 polymerase.

The subtracted NK cell library (HNKA) was constructed as follows. The biotinylated FF cRNA was mixed with the NK library, ethanol precipitated and resuspended in 5 μ l buffer (50 mM HEPES pH 7.4, 10 mM EDTA, 1.5 M NaCl, 0.2% SDS). After addition of 5 μ l formamide and heating to 95° for 1 min, the material was left to hybridize for 24 hours at 42°C. 90 μ l of 10 mM HEPES pH 7.3, 1 mM EDTA and 15 μ l streptavidin was added followed by an incubation for 20 min at 50°C. This step was repeated again after extraction with phenol/chloroform.

To the final extracted aqueous phase, the following were added: NaCl to 0.2 M, 1 μ l glycogen and 2 volumes of ethanol. After an overnight precipitation at -20°C, the DNA was pelleted and resuspended in 10 μ l water. A second round of subtraction was performed as above and the DNA transformed into *E. coli* DH105.

cDNA sequences were obtained by high-throughput sequencing of the cDNA libraries described above using a Perkin Elmer/Applied Biosystems Division Prism 377 sequencer.

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Example 2

CHARACTERIZATION OF ISOLATED CDNA SEQUENCES

The isolated cDNA sequences were compared to sequences in the EMBL DNA database using the computer algorithms FASTA and/or BLASTN. The corresponding protein sequences (DNA translated to protein in each of 6 reading frames) were compared to sequences in the SwissProt database using the computer algorithms FASTX and/or BLASTX. Comparisons of DNA sequences provided in SEQ ID NO: 1-119 to sequences in the EMBL DNA database (using FASTA) and amino acid sequences provided in SEQ ID NO: 120-197 to sequences in the SwissProt database (using FASTX) were made as of March 21, 1998. Comparisons of DNA sequences provided in SEQ ID NO: 198-274 to sequences in the EMBL DNA database (using BLASTN) and amino acid sequences provided in SEQ ID NO: 275-348 to sequences in the SwissProt database (using BLASTP) were made as of October 7, 1998. Comparisons of DNA sequences provided in SEQ ID NO: 349-372 to sequences in the EMBL DNA database (using BLASTN) and amino acid sequences provided in SEQ ID NO: 373-398 to sequences in the SwissProt database (using BLASTP) were made as of January 23, 1999. Comparisons of polynucleotide sequences provided in SEQ ID NO: 418-455 and 466-487 to sequences in the EMBL DNA database (using BLASTN) and polypeptide sequences provided in SEQ ID NO: 456-463 and 488-509 to sequences in the SwissProt database (using BLASTP) were made as of April 23, 2000. Comparisons of polynucleotide sequences provided in SEQ ID NO: 510 and 511 to sequences in the EMBL DNA database (using BLASTN) and polypeptide sequences provided in SEQ ID NO: 512 and 513 to sequences in the SwissProt database (using BLASTP) were made as of July 11, 2000. Comparisons of polynucleotide sequences provided in SEQ ID NO: 514-623 to

sequences in the EMBL66 - HTGs + ENSEMBL (May 1, 2001) DNA database (using BLASTN) and polypeptide sequences provided in SEQ ID NO: 624-725 to sequences in the SP_TR_NRDB + ENSEMBL (April 30, 2001) database (using BLASTP) were made as of May 16, 2001.

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Isolated cDNA sequences and their corresponding polypeptide sequences were computer analyzed for the presence of signal sequences identifying secreted molecules. Isolated cDNA sequences that have a signal sequence at a putative start site within the sequence are provided in SEQ ID NO: 1-44, 198-238, 349-358, 399, 418-434, 440-449 and 466-471, 516, 519, 520, 523-527, 531, 532, 535-537, 548, 555, 574-580, 585-587, 589, 593, 595, 596, 598-601, 605-607, 609, 612, 613, 615, 616 and 622. The cDNA sequences of SEQ ID NO: 1-6, 198-199, 349-352, 354, 356-358,419-428, 430-433, 440-444, 446-448, 466, 468-470, 519, 520, 523, 524, 529, 531, 532, 535-537, 579, 585, 587, 598, 605, 609, 613 and 622 were determined to have less than 75% identity (determined as described above), to sequences in the EMBL database using the computer algorithms FASTA or BLASTN, as described above. The polypeptide sequences of SEQ ID NO: 120-125, 275-276, 373-380, 382, 456, 457, 460-462, 488-493, 633, 637, 642, 683, 685, 691, 693, 703, 706, 710, 714, 717, 718, 720, 721 and 725 were determined to have less than 75% identity (determined as described above) to sequences in the SwissProt database using the computer algorithms FASTX or BLASTP, as described above.

Further sequencing of some of the isolated partial cDNA sequences resulted in the isolation of the full-length cDNA sequences provided in SEQ ID NOS: 7-14, 200-231, 372, 418-422, 441-448, 514, 516, 557-561, 567, 568, 619 and 621. The polypeptide sequences encoded by the cDNA sequences of SEQ ID NO: 7-14, 200-231, 372, 514, 516, 557-561, 567, 568, 619 and 621 are provided in SEQ ID NOS: 126-133, 277-308, 396,624, 626, 666-669, 674 and 724 respectively. The cDNA sequences of SEQ ID NO: 418-422 encode the same amino acid sequences as the cDNA sequences of SEQ ID NO: 7 and 11-14, namely SEQ ID NO: 126 and 130-133, respectively. Comparison of the full-

length cDNA sequences with those in the EMBL database using the computer algorithm FASTA or BLASTN, as described above, revealed less than 75% identity (determined as described above) to known sequences, except for the polynucleotides in SEQ ID NOS: 516, 560 and 619. Comparison of the amino acid sequences provided in SEQ ID NOS: 126-133, 277-308, 666, 668, 669 and 724 with those in the SwissProt database using the computer algorithms FASTX or BLASTP, as described above, revealed less than 75% identity (determined as described above) to known sequences.

Comparison of the polypeptide sequences corresponding to the cDNA sequences of SEQ ID NOS: 15-23 with those in the EMBL database using the computer algorithm FASTA database showed less than 75% identity (determined as described above) to known sequences. These polypeptide sequences are provided in SEQ ID NOS: 134-142.

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Further sequencing of some of the isolated partial cDNA sequences resulted in the isolation of full-length cDNA sequences provided in SEQ ID NOS: 24-44, 232-238, 423-434, 449, 466, 468-470, 475, 476 and 484. The polypeptide sequences encoded by the cDNA sequences of SEQ ID NO: 24-44, 232-238, 429, 466, 468-470, 475, 476 and 484 are provided in SEQ ID NOS: 143-163, 309-315, 456, 488, 490-492, 497, 498 and 506, respectively. The cDNA sequences of SEQ ID NO: 423-428, 430-434 and 449 encode the same polypeptide sequences as the cDNA sequences of SEQ ID NO: 27-29, 34, 35, 37, 40-44 and 238, namely SEQ ID NO: 146-148, 153, 154, 156, 159-163 and 315, respectively. These polypeptide sequences were determined to have less than 75% identity, determined as described above to known sequences in the SwissProt database using the computer algorithm FASTX.

Isolated cDNA sequences having less than 75% identity to known expressed sequence tags (ESTs) or to other DNA sequences in the public database, or whose corresponding polypeptide sequence showed less than 75% identity to known protein sequences, were computer analyzed for the presence of transmembrane domains coding for putative membrane-bound molecules. Isolated cDNA sequences that have one or more transmembrane domain(s) within the sequence are provided in SEQ ID NOS: 45-63, 239-253, 359-364, 400-402, 435, 436, 450-452, 455, 470-472, 542, 553-555, 573,

576, 581, 592, 593, 595 and 606. The cDNA sequences of SEQ ID NOS: 45-48, 239-249, 359-361, 363, 450, 451, 455, 472, 473, 553-555, 573, 576 and 592 were found to have less than 75% identity (determined as described above) to sequences in the EMBL database, using the FASTA or BLASTN computer algorithms. The polypeptide sequences encoded by the cDNA sequences of SEQ ID NO: 45-48, 239-249, 359-361, 363, 450, 451, 472, 473, 553-555, 573 and 606 (provided in SEQ ID NOS: 164-167, 316-326, 383, 385-388, 407-408, 460, 461, 494, 495, 662, 663, 664, 679, 682 and 711 respectively) were found to have less than 75% identity, determined as described above, to sequences in the SwissProt database using the FASTX or BLASTP database. The cDNA sequence of SEQ ID NO: 455 encodes the same polypeptide sequence as the cDNA sequence of SEQ ID NO: 359, namely SEQ ID NO: 383.

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Comparison of the polypeptide sequences corresponding to the cDNA sequences of SEQ ID NOS: 49-63, 250-253; 436 and 452 with those in the SwissProt database showed less than 75% identity (determined as described above) to known sequences. These polypeptide sequences are provided in SEQ ID NOS: 168-182, 327-330, 457 and 462, respectively.

Using automated search programs to screen against sequences coding for molecules reported to be of therapeutic and/or diagnostic use, some of the cDNA sequences isolated as described above in Example 1 were determined to encode polypeptides that are family members of known protein families. A family member is here defined to have at least 25% identity in the translated polypeptide to a known protein or member of a protein family. These cDNA sequences are provided in SEQ ID NOS: 64-76, 254-264, 365-369, 403, 437-439, 453, 454, 475-487, 510, 511, 514-527, 529-531, 533-536, 538-546, 548, 549, 553-559, 562, 564, 565, 567, 569-575, 577-589, 591-602, 604-612, 616-618, 621 and 622. The polypeptide sequences encoded by the cDNA sequences of SEQ ID NO: 64-76, 254-264, 365-369, 403, 438, 439, 453, 475-487, 510 and 511, 514-527, 529-531, 533-536, 538-546, 548, 549, 553-559, 562, 564, 565, 567, 569-575, 577-589, 591-602, 604-612, 616-618, 621 and 622 are provided in SEQ ID NOS: 183-195, 331-341, 389-393, 409, 458, 459, 463, 497-509, 624-637, 639-641, 643-

646, 648-656, 658, 659, 662-668, 670, 672-681, 683-707, 709-717 and 721-725, respectively. The cDNA sequences of SEQ ID NO: 437 and 454 encode the same amino acid sequences as the cDNA sequences of SEQ ID NO: 68 and 262, namely SEQ ID NO: 187 and 339, respectively. The cDNA sequences of SEQ ID NOS: 64-68, 254-264, 365-369, 437-439, 453, 454, 475-478, 480-482, 484, 485, 487, 511, 514, 515, 517-520, 522, 523, 525, 529-531, 535, 536, 538, 541, 544-546, 549, 553-559, 564, 565, 567, 569-573, 579, 587, 588, 592, 597, 598, 602, 604, 605, 608-611, 617, 621 and 622 show less than 75% identity (determined as described above) to sequences in the EMBL database using the FASTA or BLASTN computer algorithms. Similarly, the amino acid sequences of SEQ ID NOS: 183-195, 331-341, 389-393, 458, 459, 463, 497, 498, 503-505, 507-509, 512, 513, 628, 632, 633, 637, 640, 655, 662-666, 668, 672, 673, 676, 679, 683, 685, 688, 691, 693, 694, 702, 703, 706, 707, 710, 711, 713, 714, 717, 721, 722 and 725 show less than 75% identity to sequences in the SwissProt database.

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The isolated cDNA sequences encode proteins that influence the growth, differentiation and activation of several cell types, and that may usefully be developed as agents for the treatment and diagnosis of skin wounds, cancers, growth and developmental defects, and inflammatory disease. The utility for certain of the proteins of the present invention, based on similarity to known proteins, is provided in Table 2 below, together with the location of signal peptides and transmembrane domains for certain of the inventive sequences:

Table 2
FUNCTIONS OF NOVEL PROTEINS

| P/N SEQ ID NO: | A/A SEQ. ID NO. | SIMILARITY TO KNOWN PROTEINS; FUNCTION |
|----------------------|--------------------|---|
| 64, 372 | 183, 396 | Slit, a secreted molecule required for central nervous system development |
| 65 | 184 | Immunoglobulin receptor family. About 40% of leucocyte membrane polypeptides contain immunoglobulin superfamily domains |

| P/N | A/A SEQ. | |
|--------|----------|---|
| SEQ ID | ID NO. | SIMILARITY TO KNOWN PROTEINS; FUNCTION |
| NO: | 10. | |
| 66, | 185, | RIP protein kinase, a serine/threonine kinase that contains a |
| 403 | 409 | death domain to mediate apoptosis |
| 510 | 512 | doan domain to modate apoptosis |
| 67 | 186 | Extracellular protein with epidermal growth factor domain |
| 67 | 100 | capable of stimulating fibroblast proliferation |
| 60 | 107 | |
| 68, | 187 | Transforming growth factor alpha, a protein which binds |
| 437 |) | epidermal growth factor receptor and stimulates growth and |
| L | 100 | mobility of keratinocytes |
| 69 | 188 | DRS protein which has a secretion signal component and |
| | (| whose expression is suppressed in cells transformed by |
| | | oncogenes |
| 70 | 189 | A33 receptor with immunoglobulin-like domains and is |
| | | expressed in greater than 95% of colon tumors |
| 71 | 190 | Interleukin-12 alpha subunit, component of a cytokine that |
| | | is important in the immune defense against intracellular |
| } | | pathogens. IL-12 also stimulates proliferation and |
| | | differentiation of TH1 subset of lymphocytes |
| .72 | 191 | Tumor Necrosis Factor receptor family of proteins that are |
| 1 | | involved in the proliferation, differentiation and death of |
| | | many cell types including B and T lymphocytes. |
| 73 | 192 | Epidermal growth factor family proteins which stimulate |
| | ł | growth and mobility of keratinocytes and epithelial cells. |
| | | EGF is involved in wound healing. It also inhibits gastric |
| | | acid secretion. |
| 74 | 193 | Fibronectin Type III receptor family. The fibronectin III |
| | | domains are found on the extracellular regions of cytokine |
| | | receptors |
| 75 | 194 | Serine/threonine kinases (STK2_HUMAN) which |
| .5 | 1 ' | participate in cell cycle progression and signal transduction |
| 76 | 195 | Immunoglobulin receptor family |
| 254 | 331 | Receptor with immunoglobulin-like domains and homology |
| 254 | 331 | to A33 receptor which is expressed in greater than 95% of |
| | ĺ | colon tumors |
| 255 | 332 | Epidermal growth factor family proteins which stimulate |
| 233 | 1332 | growth and mobility of keratinocytes and epithelial cells. |
| | | EGF is involved in wound healing. It also inhibits gastric |
| 1 | | acid secretion. |
| 256 | 1222 | |
| 256 | 333 | Serine/threonine kinases (STK2_HUMAN) which |
| L | <u> </u> | participate in cell cycle progression and signal transduction |

| P/N SEQ ID NO: | A/A SEQ. ID NO. | SIMILARITY TO KNOWN PROTEINS; FUNCTION |
|----------------------|--------------------|---|
| . 257 | 334 | Contains protein kinase and ankyrin domains. Possible role in cellular growth and differentiation. |
| 258 | 335 | Notch family proteins which are receptors involved in cellular differentiation. |
| 259 | 336 | Extracellular protein with epidermal growth factor domain capable of stimulating fibroblast proliferation. |
| 260, 453 | 337, 463 | Fibronectin Type III receptor family. The fibronectin III domains are found on the extracellular regions of cytokine receptors. |
| 261 | 338 | Immunoglobulin receptor family |
| 262 | 339 | ADP/ATP transporter family member containing a calcium binding site. |
| 263 | 340 | Mouse CXC chemokine family members are regulators of epithelial, lymphoid, myeloid, stromal and neuronal cell migration and cancers, agents for the healing of cancers, neuro-degenerative diseases, wound healing, inflammatory autoimmune diseases like psoriasis, asthma, Crohns disease and as agents for the prevention of HIV-1 of leukocytes |
| 264 | 341 | Nucleotide-sugar transporter family member. |
| 365 | 389 | Transforming growth factor betas (TGF-betas) are secreted covalently linked to latent TGF-beta-binding proteins (LTBPs). LTBPs are deposited in the extracellular matrix and play a role in cell growth or differentiation. |
| 366 | 390 | Integrins are Type I membrane proteins that function as laminin and collagen receptors and play a role in cell adhesion. |
| 367 | 391 | Integrins are Type I membrane proteins that function as laminin and collagen receptors and play a role in cell adhesion. |
| 368 | 392 | Cell wall protein precursor. Are involved in cellular growth or differentiation. |
| 369 | 393 | HT protein is a secreted glycoprotein with an EGF-like domain. It functions as a modulator of cell growth, death or differentiation. |
| 467 | 489 | Myb proto-oncogene (c-Myb), involved in transcription regulation and activation of transcription |

| P/N | A/A SEQ. | |
|---------------|----------|--|
| SEQ ID NO: | ID NO. | SIMILARITY TO KNOWN PROTEINS; FUNCTION |
| 471 | 493 | Chondroitin sulfotransferase, a member of the HNK-1 sulfotransferase family. These molecules are involved in the pathogenesis of arteriosclerosis, and proliferation of arterial smooth muscle cells during development of arteriosclerosis. |
| 472 | 494 | 36 kDa nucleolar protein HNP36, a novel growth factor responsive gene expressed in the pituitary and parathyroid glands |
| 475 | 497 | Zinc protease is a matrix metalloproteinase whose activity is directed against components of the extracellular matrix and play an important role in the growth, metastasis and angiogenesis of tumors. |
| 476 | 498 | Diapophytoene dehydrogenase crtn-like molecule. This molecule is similar to the diapophytoene dehydrogenase crt molecule in a major photosynthesis gene cluster from the bacterium Heliobacillus mobilis |
| 477 | 499 | Protocadherin 3 family member, involved in cell to cell interactions. |
| 478 | 500 | Integrins are Type I membrane proteins that function as laminin and collagen receptors and play a role in cell adhesion. |
| 479 | 501 | Integrin family member. Integrins are Type I membrane proteins that function as laminin and collagen receptors and play a role in cell adhesion. |
| 480 | 502 | Similar to secreted HT Protein, a secreted glycoprotein with an EGF-like domain. It functions as a modulator of cell growth, death or differentiation. |
| 481 | 503 | Agrin family member: Agrin is produced by motoneurons and induces the aggregation of nicotinic acetylcholine receptors. |
| 482 | 504 | Macrophage Scavenger Receptors bind to a variety of polyanionic ligands and display complex binding characteristics. They have been implicated in various macrophage-associated processes, including atherosclerosis. |
| 483 | 505 | Similar to GARP, a member of the family of leucine-rich repeat-containing proteins involved in platelet-endothelium interactions. |
| 484 | 506 | Epidermal growth factor family proteins which stimulate growth and mobility of keratinocytes and epithelial cells. EGF is involved in wound healing. It also inhibits gastric |

| | | |
|--------|----------|---|
| P/N | A/A SEQ. | |
| SEQ ID | ID NO. | SIMILARITY TO KNOWN PROTEINS; FUNCTION |
| NO: | | |
| | , | acid secretion. |
| | | • |
| 485 | 507 | Colony stimulating growth factor family. |
| | | |
| | | |
| 486 | 508 | Cytokine receptors |
| | | |
| 407 | 500 | II 17 December to Interloylein 17 (II 17) o T cell designed |
| 487 | 509 | IL17 Receptor to Interleukin 17 (IL17), a T cell derived |
| | ļ | cytokine that may play a role in initiation or maintenance of |
| | | the inflammatory response. |
| 438 | 458 | MEGF6, a protein containing multiple EGF-like-domains. |
| | 1 | |
| 100 | 450 | |
| 439 | 459 | Protein kinase family member involved in signal |
| | | transduction. |
| 454 | | Peroxisomal calcium-dependent solute carrier, a new |
| 1 434 | | member of the mitochondrial transporter superfamily. |
| | 1 | member of the initochondria transporter superfamily. |
| 511 | 513 | Serine/threonine kinase NEK1 is a NIMA-related protein |
| | | kinase that phosphorylates serines and threonines, but also |
| | 1 | possesses tyrosine kinase activity. NEK1 has been |
| | | implicated in the control of meiosis and belongs to the |
| | | NIMA kinase subfamily. |
| | 624 62 | 6Homologue isolated from rat dermal papilla of integrin |
| 63.4 | 024 62 | |
| 514 | | alpha-11/beta-1 that is involved in muscle development and |
| | | maintaining integrity of adult muscle and other adult |
| | | tissues. Integrin alpha-11/beta-1 is a receptor for collagen |
| | L | and belongs to the integrin alpha chain family. |
| 516 | 625 | This is a secreted molecule isolated from rat dermal papillae |
| | | with a signal peptide at the N-terminus (amino acid residues |
| | Į. | 1 to 21; nucleotides 42 to 104). |
| 517 | 626 | Homologue isolated from a rat dermal papilla library of |
| | | OASIS (old astrocyte specifically-induced substance) and |
| } | | that plays a role in regulation of the response of astrocytes |
| | | to inflammation and trauma of the central nervous system |
| | | (CNS) during gliosis. The OASIS gene encodes a putative |
| } | | |
| | | transcription factor belonging to the cyclic AMP responsive |
| 1 | | element binding protein/activating transcription factor |
| | | (CREB/ATF) gene family (Honma et al., Brain Res. Mol. |
| L | <u> </u> | Brain Res. 69:93-103, 1999). |

| P/N | A/A SEQ. | OR OF A PURISH TO A PAIGURAL PROTECTION. |
|---------------|----------|---|
| SEQ ID NO: | ID NO. | SIMILARITY TO KNOWN PROTEINS; FUNCTION |
| 519 | 628 | This is a secreted molecule isolated from rat dermal papillae with a signal peptide at the N-terminus (amino acid residues 1 to 24; nucleotides 50 to 121). |
| 520 | 630 | This is a secreted molecule isolated from rat dermal papillae with a signal peptide at the N-terminus (amino acid residues 1 to 35; nucleotides 67 to 171). |
| 523 | 633 | This is a secreted molecule isolated from rat dermal papillae with a signal peptide at the N-terminus (amino acid residues 1 to 17; nucleotides 3 to 53). |
| 524 | 634 | This is a secreted molecule isolated from rat dermal papillae with a signal peptide at the N-terminus (amino acid residues 1 to 20; nucleotides 13 to 72). |
| 525, 534 | 635, 644 | Homologue isolated from a rat dermal papilla library of leucyl-specific aminopeptidase, PILS-AP and that plays role in many physiological processes as a substrate-specific peptidase. PILS is a new member of the M1 famile of Zndependent aminopeptidases that comprises members of closely related enzymes which are known to be involved in a variety of physiologically important processes. |
| 526 | 636 | This is a secreted molecule isolated from rat dermal papillae with a signal peptide at the N-terminus (amino acid residues 1 to 26; nucleotides 114 to 191). |
| 527 | 637 | This is a secreted molecule isolated from rat dermal papillae with a signal peptide at the N-terminus (amino acid residues 1 to 26; nucleotides 23 to 100). |
| 529 | 639 | This is a secreted molecule isolated from rat dermal papillae with a signal peptide at the N-terminus (amino acid residues 1 to 17; nucleotides 37 to 87). |
| 530 | 640 | This is a homologue isolated from a rat dermal papilla library of a maturase that is involved in RNA splicing. |
| 531 | 641 | This is a secreted molecule isolated from rat dermal papillae with a signal peptide at the N-terminus (amino acid residues 1 to 17; nucleotides 180 to 230). |
| 532 | 642 | This is a secreted molecule isolated from rat dermal papillae with a signal peptide at the N-terminus (amino acid residues 1 to 32; nucleotides 245 to 340). |
| 535 | 645 | This is a secreted molecule isolated from rat dermal papillae with a signal peptide at the N-terminus (amino acid residues 1 to 25; nucleotides 188 to 333). |

| P/N | A/A SEQ. | |
|---------------|----------|--|
| SEQ ID NO: | ID NO. | SIMILARITY TO KNOWN PROTEINS; FUNCTION |
| 536 | 646 | This is a secreted molecule isolated from rat dermal papillae with a signal peptide at the N-terminus (amino acid residues 1 to 21; nucleotides 185 to 247). |
| 537 | 647 | This is a secreted molecule isolated from rat dermal papillae with a signal peptide at the N-terminus (amino acid residues 1 to 24; nucleotides 129 to 200). |
| 541 | 651 | This is a homologue isolated from a rat dermal papilla library of a hepatoma-derived growth factor (HDGF) that is involved in stimulation of cell proliferation. |
| 542 | 652 | This is a receptor-like molecule isolated from rat dermal papillae with two transmembrane domains (amino acid residues 20 to 40 and 58 to 78. |
| 545 | 655 | This is a homologue isolated from a rat dermal papilla library of Link protein (LP) and that is involved in bone formation. LP plays an essential role in endochondral bone formation by stabilizing the supramolecular assemblies of aggrecan and hyaluronan (Deak et al., Cytogenet. Cell Genet. 87:75-79, 1999). |
| 548 | 658 | This is a homologue isolated from a rat dermal papilla library of thrombospondin (TSP). It is a secreted protein with a signal peptide in amino acid residues 1 to 18 (nucleotides 210 to 263). TSP is an extracellular matrix glycoprotein whose expression has been associated with a variety of cellular processes including growth and embryogenesis (Laherty et al., J. Biol. Chem. 267:3,274-3,281, 1992). |
| 553 | 662 | This is a receptor-like molecule isolated from rat dermal papillae with a transmembrane domain (amino acid residues 434 to 454. |
| 554 | 663 | This is a receptor-like molecule isolated from rat dermal papillae with a transmembrane domain (amino acid residues 546 to 566. |
| 555 | 664 | This is a homologue isolated from a rat dermal papilla library of B7-like mouse GL50 (mGL50). It is a receptor-like molecule with a signal peptide in residues 1 to 24 (nucleotides 149 to 220) and a transmembrane domain in amino acid residues 262 to 282. GL50 is a specific ligand for the ICOS receptor and this interaction functions in lymphocyte costimulation (Ling et al., J. Immunol. 164:1,653-1,657, 2000). |

| P/N SEQ ID NO: | A/A SEQ. ID NO. | SIMILARITY TO KNOWN PROTEINS; FUNCTION |
|----------------------|----------------------|---|
| 557, 558, 561-572 | 666, 667, 670-678 | These molecules are differentially expressed in stem cells but not in mature keratinocytes and are involved in developmental processes. They may be employed for diagnosis of tumors with an immature phenotype. |
| 559 | 668 | This is a homologue isolated from a mouse stem cell library of ABSENT IN MELANOMA 1 protein AIM1 and that can be used for diagnosis of tumours with an immature phenotype. AIM1 is a novel gene whose expression is associated with the experimental reversal of tumorigenicity of human malignant melanoma and belongs to the betagamma-crystallin superfamily (Ray et al., Proc. Natl. Acad. Sci. USA 94:3,229-3,234, 1997) |
| 560 | 669 | Homologue isolated from a mouse stem cell library of endothelin-convertin enzyme 2 (ECE-2) and that can be used for diagnosis of tumours with an immature phenotype. Endothelins (ET) are a family of potent vasoactive peptides that are produced from biologically inactive intermediates, termed big endothelins, via a proteolytic processing at Trp21-Val/Ile22. ECE-2, that produces mature ET-1 from big ET-1 both in vitro and in transfected cells. ECE-2 acts as an intracellular enzyme responsible for the conversion of endogenously synthesized big ET-1 at the trans-Golgi network, where the vesicular fluid is acidified (Emoto and Yanagisawa, J. Biol. Chem. 270:15,262-15,268, 1995). |
| 573 | 679 | Mouse homologue of EGF-like molecule containing mucin-like hormone receptor 2 (EMR2). The isolated molecule contains three transmembrane regions: amino acid residues 20 to 40, 66 to 86 and 92 to 112. The epidermal growth factor (EGF)-TM7 proteins [EMR1 and EMR2, F4/80, and CD97] constitute a recently defined class B GPCR subfamily and are predominantly expressed on leukocytes. These molecules possess N-terminal EGF-like domains coupled to a seven-span transmembrane (7TM) moiety via a mucin-like spacer domain (Lin et al., Genomics 67:188-200, 2000). |
| 574 | 680 | This is a murine secreted molecule with a signal peptide at the N-terminus (amino acid residues 1 to 17; nucleotides 238 to 288). |
| 575 | 681 | Mouse homologue of a glucocortocoid-inducible protein GIS5 with a signal peptide at the N-terminus (amino acid |

| P/N | A/A SEQ. | 0.1.89207989214007.0541.9 |
|---------------|----------|--|
| SEQ ID NO: | ID NO. | SIMILARITY TO KNOWN PROTEINS; FUNCTION |
| | | residues 1 to 17; nucleotides 56-106). |
| 576 | 682 | This is a murine surface receptor-like molecule with a signal peptide at the N-terminus (amino acid residues 1 to 17; nucleotides 1179 to 199) and a transmembrane domain (amino acid residues 179 to 199). |
| 577 | 683 | This is a murine secreted molecule with a signal peptide at the N-terminus (amino acid residues 1 to 16; nucleotides 55 to 102). |
| 578 | 684 | This is a murine secreted molecule with a signal peptide at the N-terminus (amino acid residues 1 to 22; nucleotides 12 to 77). |
| 579 | 685 | This is a murine secreted molecule with a signal peptide at the N-terminus (amino acid residues 1 to 17; nucleotides 82 to 132). |
| 580 | 686 | This is a murine secreted molecule with a signal peptide at the N-terminus (amino acid residues 1 to 20; nucleotides 20 to 79). |
| 581 | 687 | This is a murine receptor-like molecule with transmembrane domains at amino acid residues 50 to 70; 84 to 104; 116 to 136 and 179 to 198. |
| 585 | 691 | This is a murine secreted molecule with a signal peptide at the N-terminus (amino acid residues 1 to 20; nucleotides 260 to 319). |
| 586 | 695 | This is a murine secreted molecule with a signal peptide at the N-terminus (amino acid residues 1 to 22; nucleotides 295 to 360). |
| 587 | 693 | This is a mouse homologue of serotransferrin, also known as siderophilin or beta-1-metal binding globulin) and that is involved in iron transport. This homologue is a secreted molecule with a signal peptide at the N-terminus (amino acid residues 1 to 19; nucleotides 43 to 99). Transferrins are iron binding transport proteins which can bind two atoms of ferric iron in association with the binding of an anion, usually bicarbonate. It is responsible for the transport of iron from sites of absorption and heme degradation to those of storage and utilization. Serum transferrin may also have a further role in stimulating cell proliferation. Transferrin belongs to the transferrin family. |

| P/N | A/A SEQ. | |
|---------------|----------|---|
| SEQ ID NO: | ID NO. | SIMILARITY TO KNOWN PROTEINS; FUNCTION |
| 589 | 695 | This is a murine secreted molecule with a signal peptide at the N-terminus (amino acid residues 1 to 25; nucleotides 1 to 75). |
| . 592 | 697 | This is a murine receptor-like molecule with a transmembrane domain in amino acid residues 52 to 72. |
| 593 | 698 | Mouse homologue of channel inducing factor (CHIF) that plays a role in ion transport. The mouse homologue has a signal peptide at the N-terminus of the predicted polypeptide (amino acid residues 1 to 20; nucleotides 102 to 161) and a transmembrane domain (amino acid residues 38 to 58). CHIF evokes a potassium channel activity (Attali et al., Proc. Natl. Acad. Sci. USA 92:6092-6096, 1995). |
| 595 | 700 | Homologue of hyaluronan receptor LYVE-1 that plays a role in hyalyronan uptake. This mouse homologue has the characteristic signal peptide and transmembrane domain of a receptor. A signal peptide was identified in the isolated molecule in amino acid residues 1 to 18 (nucleotides 62 to 115) and the transmembrane domain in amino acid residues 233 to 253. The extracellular matrix glycosaminoglycan hyaluronan (HA) is an abundant component of skin and mesenchymal tissues where it facilitates cell migration during wound healing, inflammation, and embryonic morphogenesis. Both during normal tissue homeostasis and particularly after tissue injury, HA is mobilized from these sites through lymphatic vessels to the lymph nodes where it is degraded before entering the circulation for rapid uptake by the liver. LYVE-1 is a receptor for HA on the lymph vessel wall and plays a role in the transport of HA from tissue to lymph (Banerji et al., J. Cell Biol. 144:789-801,1999). |
| 596 | 701 | This is a murine secreted molecule with a signal peptide at the N-terminus (amino acid residues 1 to 21; nucleotides 7 to 69). |
| 598 | 703 | Homologue of tumor-associated glycoprotein E4 (TAA1 or TAGE4) that belongs to the immunoglobulin superfamily. This molecule has a signal peptide at the N-terminus (amino acid residues 1 to 24; nucleotides 71 to 142) and is therefore a secreted protein. |

| P/N | A/A SEQ. | | | |
|--------|----------|--|--|--|
| SEQ ID | ID NO. | SIMILARITY TO KNOWN PROTEINS; FUNCTION | | |
| NO: | | | | |
| 599 | 704 | Homologue of the LUNX protein, also known as nasopharyngeal carcinoma-related protein, tracheal epithelium enriched protein or plunc, that is expressed in epithelial cells in the airways. It has a signal peptide at the N-terminus (amino acid residues 1 to 19; nucleotides 39 to 95). Expression of LUNX is restricted to the trachea, upper airway, nasopharyngeal epithelium and salivary gland (Bingle and Bingle, Biochim. Biophys. Acta 1493:363-367, 2000). | | |
| 600 | 705 | This is a murine secreted molecule with a signal peptide at the N-terminus (amino acid residues 1 to 23; nucleotides 136 to 204. | | |
| 601 | 706 | Homologue of prenylcysteine lyase (EC 4.4.1.18) and that is involved in degradation of prenylated proteins. It has a signal peptide at the N-terminus (amino acid residues 1 to 28; nucleotides 22 to 105). Prenylcysteine lyase is a specific enzyme involved in the final step of prenylcysteine metabolism in mammalian cells. The enzyme does not require NADPH as cofactor for prenylcysteine degradation, thus distinguishing it from cytochrome P450- and flavincontaining monooxygenases that catalyze S-oxidation of thioethers (Zhang et al., J. Biol. Chem. 274:35802-35808, 1999). | | |
| 605 | 710 | Homologue of endoplasmin, endoplasmic reticulum protein 99 (ERp99), 94 kDa glucose-regulated protein (GRP94) and polymorphic tumor rejection antigen 1 (gp96). The isolated molecule has a signal peptide at the N-terminus (amino acid residue 1 to 21; nucleotides 1867 to 206). ERp99 is an abundant, conserved transmembrane glycoprotein of the endoplasmic reticulum membrane and homologous to the 90-kDa heat shock protein (hsp90) and the 94-kDa glucose regulated protein (GRP94) (Mazzarella and Green, J. Biol. Chem. 262:8875-8883, 1987). | | |
| 606 | 711 | Homologue of PILRalpha, formerly known as inhibitory receptor PIRIIalpha and that is involved in signal transduction in various cellular processes. This molecule contains a signal peptide at the N-terminal end (amino acid residues 1-21 and nucleotides 47 to 139) and a transmembrane domain at amino acid residues 191 to 211. SHP-1-mediated dephosphorylation of protein tyrosine | | |

| P/N SEQ ID NO: | A/A SEQ. ID NO. | SIMILARITY TO KNOWN PROTEINS; FUNCTION |
|----------------------|--------------------|---|
| | · | residues is central to the regulation of several cell signaling 'pathways. PILRalpha, a novel immunoreceptor tyrosine-based inhibitory motif-bearing protein, recruits SHP-1 upon tyrosine phosphorylation and is paired with the truncated counterpart PILRbeta (Mousseau et al., J. Biol. Chem. 275:4467-4474, 2000). |
| 607 | 712 | This is a murine secreted molecule with a signal peptide at the N-terminus (amino acid residues 1 to 18; nucleotides 38 to 91. |
| 609 | 714 | Homologue of retinal short-chain dehydrogenase/reductase retSDR2 that plays a role on retinal metabolism. It has a signal peptide at the N-terminus at amino acid residues 1 – 29 (nucleotides 302 to 388). Retinol dehydrogenases (RDH) catalyze the reduction of all-trans-retinal to all-trans-retinol within the photoreceptor outer segment in the regeneration of bleached visual pigments (Haeseleer et al., J. Biol. Chem. 273:21790-21799, 1998) |
| 612 | 717 | This is a murine secreted molecule with a signal peptide at the N-terminus (amino acid residues 1 to 22; nucleotides 6 to 71. |
| 613 | 718 | This is a murine secreted molecule with a signal peptide at the N-terminus (amino acid residues 1 to 25; nucleotides 210 to 284. |
| 615 | 720 | This is a murine secreted molecule with a signal peptide at the N-terminus (amino acid residues 1 to 16; nucleotides 70 to 117. |
| 616 | 721 | This is a murine secreted molecule with a signal peptide at the N-terminus (amino acid residues 1 to 18; nucleotides 1 to 54. |

The locations of open reading frames (ORFs) within certain of the inventive cDNA sequences are shown in Table 3, below.

Table 3

LOCATION OF OPEN READING FRAMES

5

| SEQ ID NO | | SEQ ID NO |
|----------------|-------------|-------------|
| Polynucleotide | ORF | Polypeptide |
| 514 | 1-2,067 | 624 |
| 515 | 2-730 | 625 |
| 516 | 42-1,772 | 626 |
| 517 | 1-681 | 627 |
| . 518 | 170-416 | 628 |
| 519 | 50-770 | 629 |
| 520 | 67-708 | 630 |
| 521 | 110-613 | 631 |
| 522 | 41-457 | 632 |
| 523 | 3-230 | 633 |
| 524 | 13-573 | 634 |
| 525 | 64-2,856 | 635 |
| 526 | 114-599 | 636 |
| 527 | 23-520 | 637 |
| 528 | 953-1,138 | 638 |
| 529 | 37-687 | 639 |
| 530 | 145-366 | 640 |
| 531 | 180-1,508 | 643 |
| 532 | 245-442 | 642 |
| 533 | 125-595 | 643 . |
| 534 | 64-2,856 | 644 |
| 535 | 188-727 | 645 |
| 536 | 185-1,081 | 646 |
| 537 | 129-308 | 647 |
| 538 | 32-853 | 648 |
| 539 | 2-268 | 649 |
| 540 | 3-875 | 650 |
| 541 | 284-892 | 651 |
| 542 | 37-276 | 652 |
| 543 | 127-1,794 | 653 |
| 544 | 1-735 | 654 |
| 545 | 142-939 | 655 |
| 546 | 51-1,082 | 656 |
| 547 | 143-328 | 657 |
| 548 | 210-3,728 | 658 |
| 549 | 26-1,354 | 659 |
| 551 | 1,236-1,892 | 660 |
| 552 | 853-1,178 | 661 |

| SEQ ID NO Polynucleotide | ORF | SEQ ID NO Polypeptide |
|-----------------------------|-------------|--------------------------|
| 553 | 54-1,356 | 662 |
| 554 | 637-2,244 | 663 |
| 555 | 149-1,072 | 664 |
| 556 | 18-449 | 665 |
| 557 | 275-1,171 | 666 |
| 558 | 453-1,133 | 667 |
| 559 | 104-2,449 | 668 |
| 560 | 463-687 | 669 |
| 562 | 1-1,107 | 670 · |
| 563 | 2-883 | 671 |
| 564 | 188-2,902 | 672 |
| 565 | 3-524 | 673 |
| 567 | 2,584-3,996 | 674 |
| 569 | 1-960 | 675 |
| 570 | 315-599 | 676 |
| 571 | 1-414 | 677 |
| 572 | 806-1,912 | 678 |
| . 573 | 120-752- | 679 |
| 574 | 2381,359 | 680 |
| 575 | 56-1,456 | 681 |
| 576 | 13-645 | 682 |
| 577 | 55-1,323 | 683 |
| 578 | 12-698 | 684 |
| 579 | 82-810 | 685 |
| 580 | 20-586 | 686 |
| 581 | 65-808 | 687 |
| 582 | 369-761 | 688 |
| 583 | 1-769 | 689 |
| 584 | 164-1,321 | 690 |
| 585 | 260-1,489 | 691 |
| 586 | 295-1,131 | 692 |
| 587 | 43-2,136 | . 693 |
| . 588 | 1-1,203 | 694 |
| 589 | 1-525 | 695 |
| 591 | 1-584 | 696 |
| 592 | 1-522 | 697 |
| 593 | 102-368 | 698 |
| 594 | 1-517 | 699 |

| SEQ ID NO | | SEQ ID NO |
|----------------|-------------|-------------|
| Polynucleotide | ORF | Polypeptide |
| 595 | 62-1,018 | 700 |
| 596 | 7-282 | 701 |
| 597 | 1-736 | 702 |
| 598 | 71-1,297 | 703 |
| 599 | 39-875 | 704 |
| 600 | 136-930 | 705 |
| 601 | 22-1,539 | 706 |
| 602 | 69-521 | 707 |
| 603 . | 104-448 | 708 |
| 604 | 1-399 | 709 |
| 605 | 3,068-5,476 | 710 |
| 606 | 47-721 | 711 |
| 607 | 38-439 | 712 |
| 608 | 1-1,656 | 713 |
| 609 | 302-1,327 | 714 |
| 610 | 845-1,447 | 715 |
| 611 | 975-1,375 | 716 |
| 612 | 6-272 | 717 |
| 613 | 210-464 | 718 |
| 614 | 462-869 | 719 . |
| 615 | 70-459 | 720 |
| 616 | 1-1,107 | 721 |
| 617 | 1-349 | 722 |
| 618 | 93-528 | 723 |
| 621 | 380-1,033 | 724 |
| 622 | 43-2,115 | 725 |

The cDNA sequences of SEQ ID NO: 514, 515, 516, 557, 558, 559, 560, 561, 567, 568, 619 and 621 are extended sequences of SEQ ID NO: 479, 480, 353, 91, 108, 82, 92, 81, 105, 90, 362 and 360, respectively. SEQ ID NO: 516, 520, 521, 523, 525, 526, 529, 534-536, 541-543, 546, 548, 549, 557, 574, 575, 577-581, 584-587, 589, 593, 595, 596, 598-601, 605, 607, 609, 610, 614, 616 and 622 represent full-length cDNA sequences.

The polynucleotide sequences of SEQ ID NOS: 77-117, 265-267, 404-405 and 557-611 are differentially expressed in either keratinocyte stem cells (KSCL) or in transit amplified cells (TRAM) on the basis of the number of times these sequences exclusively appear in either one of the above two libraries; more than 9 times in one and none in the other (Audic S. and Claverie J-M, *Genome Research*, 7:986-995, 1997). The sequences of SEQ ID NOS: 77-89, 265-267 and 365-369 were determined to have less than 75% identity to sequences in the EMBL database using the computer algorithm FASTA or BLASTN, as described above. The polypeptide sequences encoded by the cDNA sequences of SEQ ID NO: 77-117, 265-267, 404-405 and 557-611 are provided in SEQ ID NOS: 666-718. The amino acid sequences of SEQ ID NOS: 666, 668, 669, 671-673, 675, 676, 679, 682, 683, 685, 688, 690, 691, 693, 694, 702, 703, 706-708, 710, 711, 713 and 714 show less than 75% identity to sequences in the SwissProt database.

The polypeptides encoded by these polynucleotide sequences have utility as markers for identification and isolation of these cell types, and antibodies against these proteins may be usefully employed in the isolation and enrichment of these cells from complex mixtures of cells. Isolated polynucleotides and their corresponding proteins exclusive to the stem cell population can be used as drug targets to cause alterations in regulation of growth and differentiation of skin cells, or in gene targeting to transport specific therapeutic molecules to skin stem cells.

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Example 3

ISOLATION AND CHARACTERIZATION OF THE HUMAN HOMOLOG OF MUTRI

The human homolog of muTR1 (SEQ ID NO: 68), obtained as described above in Example 1, was isolated by screening 50,000 pfu's of an oligo dT primed HeLa cell cDNA library. Plaque lifts, hybridization, and screening were performed using standard molecular biology techniques (Sambrook, J, Fritsch, EF and Maniatis, T, eds., *Molecular Cloning: A Laboratory Manual*, 2nd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor: New York, 1989). The determined cDNA sequence of the isolated human homolog (huTR1) is provided in SEQ ID NO: 118, with the corresponding

polypeptide sequence being provided in SEQ ID NO: 196. The library was screened using an [α ³²P]-dCTP labeled double stranded cDNA probe corresponding to nucleotides 1 to 459 of the coding region within SEQ ID NO: 118.

**The polypeptide sequence of huTR1 has regions similar to Transforming Growth Factor-alpha, indicating that this protein functions like an epidermal growth factor (EGF). EGF family members exist in a functional form as small peptides. Alignment of the functional peptides of the EGF family with SEQ ID NO: 196 revealed that an internal segment of SEQ ID NO: 196 (amino acids 54-104) shows greater than 40% identity to the active peptides of EGF, TGF-alpha and Epiregulin. The active peptides of the EGF family are sufficient for activity and contain several conserved residues critical for the maintenance of this activity. These residues are retained in huTR1. This EGF-like protein will serve to stimulate keratinocyte growth and motility, and to inhibit the growth of epithelial-derived cancer cells. This novel gene and its encoded protein may thus be used as agents for the healing of wounds and regulators of epithelial-derived cancers.

Analysis of RNA transcripts by Northern Blotting

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Northern analysis to determine the size and distribution of mRNA for huTR1 was performed by probing human tissue mRNA blots (Clontech) with a probe comprising nucleotides 93-673 of SEQ ID NO: 118, radioactively labeled with $[\alpha^{32}P]$ -dCTP. Prehybridization, hybridization, washing and probe labeling were performed as described in Sambrook, *et al.*, *Ibid.* mRNA for huTR1 was 3.5-4kb in size and was observed to be most abundant in heart and placenta, with expression at lower levels being observed in spleen, thymus, prostate and ovary (Fig. 1).

The high abundance of mRNA for huTR1 in the heart and placenta indicates a role for huTR1 in the formation or maintenance of blood vessels, as heart and placental tissues have an increased abundance of blood vessels, and therefore endothelial cells, compared to other tissues in the body. This, in turn, demonstrates a role for huTR1 in angiogenesis and vascularization of tumors. This is supported by the ability of

Transforming Growth Factor-alpha and EGF to induce *de novo* development of blood vessels (Schreiber, *et al.*, *Science* 232:1250-1253, 1986) and stimulate DNA synthesis in endothelial cells (Schreiber, *et al.*, *Science* 232:1250-1253, 1986), and their over-expression in a variety of human tumors.

Purification of muTR1 and huTR1

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Polynucleotides 177-329 of muTR1 (SEQ ID NO: 268), encoding amino acids 53-103 of muTR1 (SEQ ID NO: 342), and polynucleotides 208-360 of huTR1 (SEQ ID NO: 269), encoding amino acids 54-104 of huTR1 (SEQ ID NO: 343), were cloned into the bacterial expression vector pProEX HT (BRL Life Technologies), which contains a bacterial leader sequence and N-terminal 6xHistidine tag. These constructs were transformed into competent XL1-Blue *E. coli* as described in Sambrook et al., *Ibid*.

Starter cultures of these recombinant XL1-Blue *E. coli* were grown overnight at 37°C in Terrific broth containing 100 µg/ml ampicillin. This culture was spun down and used to inoculate 500 ml culture of Terrific broth containing 100 µg/ml ampicillin. Cultures were grown until the OD₅₉₅ of the cells was between 0.4 and 0.8, whereupon IPTG was added to 1 mM. Cells were induced overnight and bacteria were harvested by centrifugation.

Both the polypeptide of muTR1 (SEQ ID NO: 342; referred to as muTR1a) and that of huTR1 (SEQ ID NO: 343; referred to as huTR1a) were expressed in insoluble inclusion bodies. In order to purify the polypeptides muTR1a and huTR1a, bacterial cell pellets were re-suspended in lysis buffer (20 mM Tris-HCl pH 8.0, 10 mM beta mercaptoethanol, 1 mM PMSF). To the lysed cells, 1% NP40 was added and the mix incubated on ice for 10 minutes. Lysates were further disrupted by sonication on ice at 95W for 4 x 15 seconds and then centrifuged for 15 minutes at 14,000 rpm to pellet the inclusion bodies.

The resulting pellet was re-suspended in lysis buffer containing 0.5% w/v CHAPS and sonicated on ice for 5-10 seconds. This mix was stored on ice for 1 hour, centrifuged at 14,000 rpm for 15 minutes at 4 °C and the supernatant discarded. The pellet was once

more re-suspended in lysis buffer containing 0.5% w/v CHAPS, sonicated, centrifuged and the supernatant removed as before. The pellet was re-suspended in solubilizing buffer (6 M Guanidine HCl, 0.5 M NaCl, 20 mM Tris HCl, pH 8.0), sonicated at 95 W for 4 x 15 seconds and then centrifuged for 20 minutes at 14,000 rpm and 4 °C to remove debris. The supernatant was stored at 4 °C until use.

Polypeptides muTR1a and huTR1a were purified by virtue of the N-terminal 6x Histidine tag contained within the bacterial leader sequence, using a Nickel-Chelating Sepharose column (Amersham Pharmacia, Uppsala, Sweden) and following the manufacturer's recommended protocol. In order to refold the proteins once purified, the protein solution was added to 5x its volume of refolding buffer (1 mM EDTA, 1.25 mM reduced glutathione, 0.25 mM oxidised glutathione, 20 mM Tris-HCl, pH 8.0) over a period of 1 hour at 4 °C. The refolding buffer was stirred rapidly during this time, and stirring continued at 4 °C overnight. The refolded proteins were then concentrated by ultrafiltration using standard protocols.

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Biological Activities of Polypeptides muTR1a and huTR1a

muTR1 and huTR1 are novel members of the EGF family, which includes EGF, TGFα, epiregulin and others. These growth factors are known to act as ligands for the EGF receptor. The pathway of EGF receptor activation is well documented. Upon binding of a ligand to the EGF receptor, a cascade of events follows, including the phosphorylation of proteins known as MAP kinases. The phosphorylation of MAP kinase can thus be used as a marker of EGF receptor activation. Monoclonal antibodies exist which recognize the phosphorylated forms of 2 MAP kinase proteins – ERK1 and ERK2.

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In order to examine whether purified polypeptides of muTR1a and huTR1a act as a ligand for the EGF receptor, cells from the human epidermal carcinoma cell line A431 (American Type Culture Collection, No. CRL-1555, Manassas, Virginia) were seeded into 6 well plates, serum starved for 24 hours, and then stimulated with purified muTR1a or huTR1a for 5 minutes in serum free conditions. As a positive control, cells were

stimulated in the same way with 10 to 100 ng/ml TGF-alpha or EGF. As a negative control, cells were stimulated with PBS containing varying amounts of LPS. Cells were immediately lysed and protein concentration of the lysates estimated by Bradford assay. 15 µg of protein from each sample was loaded onto 12% SDS-PAGE gels. The proteins were then transferred to PVDF membrane using standard techniques.

For Western blotting, membranes were incubated in blocking buffer (10mM Tris-HCl, pH 7.6, 100 mM NaCl, 0.1% Tween-20, 5% non-fat milk) for 1 hour at room temperature. Rabbit anti-Active MAP kinase pAb (Promega, Madison, Wisconsin) was added to 50 ng/ml in blocking buffer and incubated overnight at 4 °C. Membranes were washed for 30 mins in blocking buffer minus non-fat milk before being incubated with anti rabbit IgG-HRP antibody, at a 1:3500 dilution in blocking buffer, for 1 hour at room temperature. Membranes were washed for 30 minutes in blocking buffer minus non-fat milk, then once for 5 minutes in blocking buffer minus non-fat milk and 0.1% Tween-20. Membranes were then exposed to ECL reagents for 2 min, and then autoradiographed for 5 to 30 min.

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As shown in Fig. 2, both muTR1a and huTR1a were found to induce the phosphorylation of ERK1 and ERK2 over background levels, indicating that muTR1 and huTR1 act as ligands for a cell surface receptor that activates the MAP kinase signaling pathway, possibly the EGF receptor. As shown in Fig. 11, huTR1a was also demonstrated to induce the phosphorylation of ERK1 and ERK2 in CV1/EBNA kidney epithelial cells in culture, as compared with the negative control. These assays were conducted as described above. This indicates that huTR1a acts as a ligand for a cell surface receptor that activates the MAP kinase signaling pathway, possibly the EGF receptor in HeLa and CV1/EBNA cells.

The ability of muTR1a to stimulate the growth of neonatal foreskin (NF) keratinocytes was determined as follows. NF keratinocytes derived from surgical discards were cultured in KSFM (BRL Life Technologies) supplemented with bovine pituatary extract (BPE) and epidermal growth factor (EGF). The assay was performed in 96 well flat-bottomed plates in 0.1 ml unsupplemented KSFM. MuTR1a, human

transforming growth factor alpha (huTGF α) or PBS-BSA was titrated into the plates and 1 x 10³ NF keratinocytes were added to each well. The plates were incubated for 5 days in an atmosphere of 5% CO₂ at 37⁰C. The degree of cell growth was determined by MTT dye reduction as described previously (*J. Imm. Meth.* 93:157-165, 1986). As shown in Fig. 3, both muTR1a and the positive control human TGF α stimulated the growth of NF keratinocytes, whereas the negative control, PBS-BSA, did not.

The ability of muTR1a and huTR1a to stimulate the growth of a transformed human keratinocyte cell line, HaCaT, was determined as follows. The assay was performed in 96 well flat-bottomed plates in 0.1 ml DMEM (BRL Life Technologies) supplemented with 0.2% FCS. MuTR1a, huTR1a and PBS-BSA were titrated into the plates and 1 x10³ HaCaT cells were added to each well. The plates were incubated for 5 days in an atmosphere containing 10% CO₂ at 37⁰C. The degree of cell growth was determined by MTT dye reduction as described previously (*J. Imm. Meth.* 93:157-165, 1986). As shown in Fig. 4, both muTR1a and huTR1a stimulated the growth of HaCaT cells, whereas the negative control PBS-BSA did not.

The ability of muTR1a and huTR1a to inhibit the growth of A431 cells was determined as follows. Polypeptides muTR1a (SEQ ID NO: 342) and huTR1a (SEQ ID NO: 343) and PBS-BSA were titrated as described previously (*J. Cell. Biol.* 93:1-4, 1982), and cell death was determined using the MTT dye reduction as described previously (*J. Imm. Meth.* 93:157-165, 1986). Both muTR1a and huTR1a were found to inhibit the growth of A431 cells, whereas the negative control PBS-BSA did not (Fig. 5).

These results indicate that muTR1 and huTR1 stimulate keratinocyte growth and motility, inhibit the growth of epithelial-derived cancer cells, and play a rolê in angiogenesis and vascularization of tumors. This novel gene and its encoded protein may thus be developed as agents for the healing of wounds, angiogenesis and regulators of epithelial-derived cancers.

Upregulation of huTR1 and mRNA expression

HeLa cells (human cervical adenocarcinoma) were seeded in 10 cm dishes at a concentration of 1 x 10⁶ cells per dish. After incubation overnight, media was removed and replaced with media containing 100 ng/ml of muTR1, huTR1, huTGFα, or PBS as a negative control. After 18 hours, media was removed and the cells lysed in 2 ml of TRIzol reagent (Gibco BRL Life Technologies, Gaithersburg, Maryland). Total RNA was isolated according to the manufacturer's instructions. To identify mRNA levels of huTR1 from the cDNA samples, 1 μl of cDNA was used in a standard PCR reaction. After cycling for 30 cycles, 5 μl of each PCR reaction was removed and separated on a 1.5% agarose gel. Bands were visualized by ethidium bromide staining. As can be seen from Fig. 12, both mouse and human TR1 up-regulate the mRNA levels of huTR1 as compared with cells stimulated with the negative control of PBS. Furthermore, TGFα can also up-regulate the mRNA levels of huTR1.

These results indicate that TR1 is able to sustain its own mRNA expression and subsequent protein expression, and thus is expected to be able to contribute to the progression of diseases such as psoriasis where high levels of cytokine expression are involved in the pathology of the disease. Furthermore, since $TGF\alpha$ can up-regulate the expression of huTR1, the up-regulation of TR1 mRNA may be critical to the mode of action of $TGF\alpha$.

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Serum response element reporter gene assay

The serum response element (SRE) is a promoter element required for the regulation of many cellular immediate-early genes by growth. Studies have demonstrated that the activity of the SRE can be regulated by the MAP kinase signaling pathway. Two cell lines, PC12 (rat pheochromocytoma – neural tumor) and HaCaT (human transformed keratinocytes), containing eight SRE upstream of an SV40 promotor and luciferase reporter gene were developed in-house. 5 x 10³ cells were aliquoted per well of 96 well plate and grown for 24 hours in their respective media. HaCaT SRE cells were grown in 5% fetal bovine serum (FBS) in D-MEM supplemented with 2mM L-glutamine (Sigma,

St. Louis, Missouri), 1mM sodium pyruvate (BRL Life Technologies), 0.77mM L-asparagine (Sigma), 0.2mM arginine (Sigma), 160mM penicillin G (Sigma), 70mM dihydrostreptomycin (Roche Molecular Biochemicals, Basel, Switzerland), and 0.5 mg/ml geneticin (BRL Life Technologies). PC12 SRE cells were grown in 5% fetal bovine serum in Ham F12 media supplemented with 0.4 mg/ml geneticin (BRL Life Technologies). Media was then changed to 0.1% FBS and incubated for a further 24 hours. Cells were then stimulated with a titration of TR1 from 1 µg/ml. A single dose of basic fibroblast growth factor at 100 ng/ml (R&D Systems, Minneapolis, Minnesota) or epidermal growth factor at 10 ng/ml (BRL Life Technologies) was used as a positive control. Cells were incubated in the presence of muTR1 or positive control for 6 hours, washed twice in PBS and lysed with 40 µl of lysis buffer (Promega). 10 µl was transferred to a 96 well plate and 10 µl of luciferase substrate (Promega) added by direct injection into each well by a Victor² fluorimeter (Wallac), the plate was shaken and the luminescence for each well read at 3x1 sec Intervals. Fold induction of SRE was calculated using the following equation: Fold induction of SRE = Mean relative luminescence of agonist/Mean relative luminescence of negative control.

As shown in Fig. 13, muTR1 activated the SRE in both PC-12 (Fig. 13A) and HaCaT (Fig. 13B) cells. This indicates that HaCaT and PC-12 cells are able to respond to muTR1 protein and elicit a response. In the case of HaCaT cells, this is a growth response. In the case of PC-12 cells, this may be a growth, a growth inhibition, differentiation, or migration response. Thus, TR1 may be important in the development of neural cells or their differentiation into specific neural subsets. TR1 may also be important in the development and progression of neural tumors.

25 Inhibition by the EGF receptor assay

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The HaCaT growth assay was conducted as previously described, with the following modifications. Concurrently with the addition of EGF and TR1 to the media, anti-EGF Receptor (EGFR) antibody (Promega, Madison, Wisconsin) or the negative

control antibody, mouse IgG (PharMingen, San Diego, California), were added at a concentration of 62.5 ng/ml.

As seen in Fig. 14, an antibody which blocks the function of the EGFR inhibited the mitogenicity of TR1 on HaCaT cells. This indicates that the EGFR is crucial for transmission of the TR1 mitogenic signal on HaCaT cells. TR1 may bind directly to the EGF receptor. TR1 may also bind to any other members of the EGFR family (for example, ErbB-2, -3, and/or -4) that are capable of heterodimerizing with the EGFR.

Splice variants of huTR1

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A variant of huTR1 was isolated from the same library as huTR1, following the same protocols. The sequence referred to as huTR1-1 (also known as TR1δ) is a splice variant of huTR1 and consists of the ORF of huTR1 minus amino acids 15 to 44 and 87 to 137. These deletions have the effect of deleting part of the signal sequence and following amino terminal linker sequence, residues following the second cysteine residue of the EGF motif and the following transmembrane domain. However, cysteine residue 147 (huTR1 ORF numbering) may replace the deleted cysteine and thus the disulphide bridges are likely not affected. Therefore, huTR1-1 is an intracellular form of huTR1. It functions as an agonist or an antagonist to huTR1 or other EGF family members, including EGF and TGFα. The determined nucleotide sequence of huTR1-1, is given in SEQ ID NO: 412, with the corresponding amino acid sequence being provided in SEQ ID NO: 415.

Four additional splice variants of huTr1 were isolated by PCR on first strand cDNA made from RNA isolated from HeLa cells by standard protocols. These splice variants of huTR1 are referred to as TR1-2 (also known as TR1 β), TR1-3 (also known as TR1 γ), TR1 ϵ and TR1 ϕ .

TR1-2 consists of the ORF of huTR1 minus amino acids 95 to 137. This deletion has the effect of deleting the transmembrane domain. Therefore TR1-2 is a secreted form of huTR1 and binds with equal or greater affinity to the TR1 receptor as huTR1, since the EGF domain remains intact. It functions as an agonist or an antagonist to huTR1 or other

EGF family members, including EGF and TGFα. The determined cDNA sequence of TR1-2 is given in SEQ ID NO: 410 and the corresponding amino acid sequence in SEQ ID NO: 413.

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TR1-3 consists of the ORF of huTR1 minus amino acids 36 to 44 and amino acids 86 to 136. These deletions have the effect of deleting part of the amino terminal linker sequence, residues following the second cysteine of the EGF motif and the following transmembrane domain. However, cysteine residue 147 (huTR1 ORF numbering) may replace the deleted cysteine and thus the disulphide bridges are likely not affected. Therefore, TR1-3 is also a secreted form of huTR1 and functions as an agonist or an antagonist to huTR1 or other EGF family members, including EGF and TGF α . The determined cDNA sequence of TR1-3 is given in SEQ ID NO: 411 and the corresponding amino acid sequence is SEQ ID NO: 414.

TR1ɛ consists of the ORF of huTR1 minus amino acids 86 to 136. This deletion has the effect of deleting residues following the second cysteine of the EGF motif and the transmembrane domain. However, cysteine residue 147 (huTR1 ORF numbering) may replace the deleted cysteine and thus the disulphide bridges are likely not affected. Therefore, TR1ɛ is also a secreted form of huTR1 and functions as an agonist or an antagonist to huTR1 or other EGF family members, including EGF and TGF α . The determined cDNA sequence of TR1ɛ is given in SEQ ID NO: 371 and the corresponding polypeptide sequence in SEQ ID NO: 395.

TR1φ consists of the ORF of huTR1 minus amino acids 36 to 44 and amino acids 95 to 136. These deletions have the effect of deleting part of the amino terminal linker sequence and the transmembrane domain. Therefore TR1φ is a secreted form of huTR1 and binds with equal or greater affinity to the TR1 receptor as huTR1, since the EGF domain remains intact. It functions as an agonist or an antagonist to huTR1 or other EGF family members, including EGF and TGFα. The determined nucleotide sequence of TR1φ is given in SEQ ID NO: 416 and the corresponding polypeptide sequence in SEQ ID NO: 417.

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Example 4

IDENTIFICATION, ISOLATION AND CHARACTERIZATION OF DP3

A partial cDNA fragment, referred to as DP3, was identified by differential display RT-PCR (modified from Liang P and Pardee AB, *Science* 257:967-971, 1992) using mRNA from cultured rat dermal papilla and footpad fibroblast cells, isolated by standard cell biology techniques. This double stranded cDNA was labeled with $[\alpha^{32}P]$ -dCTP and used to identify a full length DP3 clone by screening 400,000 pfu's of an oligo dT-primed rat dermal papilla cDNA library. The determined full-length cDNA sequence for DP3 is provided in SEQ ID NO: 119, with the corresponding amino acid sequence being provided in SEQ ID NO: 197. Plaque lifts, hybridization and screening were performed using standard molecular biology techniques.

Example 5 ISOLATION AND CHARACTERIZATION OF KS1

25 Analysis of RNA transcripts by Northern Blotting

Northern analysis to determine the size and distribution of mRNA for muKS1 (SEQ ID NO: 263) was performed by probing murine tissue mRNA blots with a probe consisting of nucleotides 268-499 of muKS1, radioactively labeled with $[\alpha^{32}P]$ -dCTP. Prehybridization, hybridization, washing, and probe labeling were performed as

described in Sambrook, et al., Ibid. mRNA for muKS1 was 1.6 kb in size and was observed to be most abundant in brain, lung, or any muscle, and heart. Expression could also be detected in lower intestine, skin, bone marrow, and kidney. No detectable signal was found in testis, spleen, liver, thymus, stomach.

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Human homologue of muKS1

MuKS1 (SEQ ID NO: 263) was used to search the EMBL database (Release 50, plus updates to June, 1998) to identify human EST homologues. The top three homologies were to the following ESTs: accession numbers AA643952, HS1301003 and AA865643. These showed 92.63% identity over 285 nucleotides, 93.64% over 283 nucleotides and 94.035% over 285 nucleotides, respectively. Frame shifts were identified in AA643952 and HS1301003 when translated. Combination of all three ESTs identified huKS1 (SEQ ID NO: 270) and translated polypeptide SEQ ID NO: 344. Alignment of muKS1 and huKS1 polypeptides indicated 95% identity over 96 amino acids.

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Identification of KSCL009274 cDNA sequence

A directionally cloned cDNA library was constructed from immature murine keratinocytes and submitted for high-throughput sequencing. Sequence data from a clone designated KDCL009274 showed 35% identity over 72 amino acids with rat macrophage inflammatory protein-2B (MIP-2B) and 32% identity over 72 amino acids with its murine homologue. The insert of 1633bp (SEQ ID NO: 464; Fig. 15A) contained an open reading frame of 300bp with a 5' untranslated region of 202bp and a 3' untranslated region of 1161bp. A poly-adenylation signal of AATAAA is present 19 base pairs upstream of the poly-A tail. The mature polypeptide (SEQ ID NO: 465) is 77 amino acids in length containing 4 conserved cysteines with no ELR motif. The putative signal peptide cleavage site beween GLY 22 and Ser 23 was predicted by the hydrophobicity profile. This putative chemokine was identical to KS1. The full length sequence was screened against the EMBL database using the BLAST program and showed some identity at the nucleotide level with human EST clones AA643952, AA865643, and

HS1301003, respectively. A recently described human CXC chemokine, BRAK, has some identity with KS1 at the protein level. The alignment of KS1 (referred to in Fig. 15B as KLF-1), BRAK, and other murine α -chemokines is shown in Fig. 15B. The phylogenetic relationship between KS1 and other α -chemokine family members was determiend using the Phylip program. KS1 and BRAK demonstrate a high degree of divergence from the other α -chemokines, supporting the relatively low homology shown in the multiple alignment.

Bacterial expression and purification of muKS1 and huKS1

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Polynucleotides 269-502 of muKS1 (SEQ ID NO: 271), encoding amino acids 23-99 of polypeptide muKS1 (SEQ ID NO: 345), and polynucleotides 55-288 of huKS1 (SEQ ID NO: 272), encoding amino acids 19-95 of polypeptide huKS1 (SEQ ID NO: 346), were cloned into the bacterial expression vector pET-16b (Novagen, Madison, Wisconsin), which contains a bacterial leader sequence and N-terminal 6xHistidine tag. These constructs were transformed into competent XL1-Blue *E. coli* as described in Sambrook et al., *Ibid*.

Starter cultures of recombinant BL 21 (DE3) *E. coli* (Novagen) containing SEQ ID NO: 271 (muKS1a) and SEQ ID NO: 272 (huKS1a) were grown in NZY broth containing 100 μg/ml ampicillin (Gibco-BRL Life Technologies) at 37°C. Cultures were spun down and used to inoculate 800 ml of NZY broth and 100 μg/ml ampicillin. Cultures were grown until the OD₅₉₅ of the cells was between 0.4 and 0.8. Bacterial expression was induced for 3 hours with 1 mM IPTG. Bacterial expression produced an induced band of approximately 15kDa for muKS1a and huKS1a.

MuKS1a and huKS1a were expressed in insoluble inclusion bodies. In order to purify the polypeptides, bacterial cell pellets were re-suspended in lysis buffer (20 mM Tris-HCl pH 8.0, 10 mM βMercaptoethanol, 1 mM PMSF). To the lysed cells, 1% NP-40 was added and the mix incubated on ice for 10 minutes. Lysates were further disrupted by sonication on ice at 95 W for 4 x 15 seconds and then centrifuged for 10 minutes at 18,000 rpm to pellet the inclusion bodies.

The pellet containing the inclusion bodies was re-suspended in lysis buffer containing 0.5% w/v CHAPS and sonicated for 5-10 seconds. This mix was stored on ice for 1 hour, centrifuged at 14000 rpm for 15 minutes at 4°C and the supernatant discarded. The pellet was once more re-suspended in lysis buffer containing 0.5% w/v CHAPS, sonicated, centrifuged, and the supernatant removed as before. The pellet was resuspended in solubilizing buffer (6 M guanidine HCl, 0.5 M NaCl, 20 mM Tris-HCl pH 8.0), sonicated at 95W for 4 x 15 seconds and centrifuged for 10 minutes at 18000 rpm and 4°C to remove debris. The supernatant was stored at 4°C. MuKS1a and huKS1a were purified by virtue of the N-terminal 6x histidine tag contained within the bacterial leader sequence, using a Nickel-Chelating sepharose column (Amersham Pharmacia, Uppsala, Sweden) and following the manufacturer's protocol. Proteins were purified twice over the column to reduce endotoxin contamination. In order to re-fold the proteins once purified, the protein solution was dialysed in a 4 M-2 M urea gradient in 20 mM tris-HCl pH 7.5 + 10% glycerol overnight at 4°C. The protein was then further dialysed 2x against 2 litres of 20 mM Tris-HCl pH 7.5 + 10% (w/v) glycerol. Preparations obtained were greater than 95% pure as determined by SDS-PAGE. Endotoxin contamination of purified proteins were determined using a limulus amebocyte lysate assay kit (BIO Whittaker, Walkersville, MD). Endotoxin levels were <0.1 ng/µg of protein. Internal amino acid sequencing was performed on tryptic peptides of KS1.

An Fc fusion protein was produced by expression in HEK 293 T cells. 35µg of KLF-1plGFc DNA to transfect 6 x 10⁶ cells per flask, 200 mls of Fc containing supernatant was produced. The Fc fusion protein was isolated by chromatography using an Affiprep protein A resin (0.3 ml column, Biorad). After loading, the column was washed with 15 mls of PBS, followed by a 5 ml wash of 50 mM Na citrate pH 5.0. The protein was then eluted with 6 column volumes of 50 mM Na citrate pH 2.5, collecting 0.3 ml fractions in tubes containing 60µl of 2M Tris-HCI pH 8.0. Fractions were analyzed by SDS-PAGE.

Peptide sequencing of muKS1 and huKS1

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Bacterially expressed muKS1 and huKS1 were separated on polyacrylamide gels and induced bands of 15 kDa were identified. The predicted size of muKS1 is 9.4 kDa. To obtain the amino acid sequence of the 15 kDa bands, 20 µg recombinant muKS1 and huSK1 was resolved by SDS-PAGE and electroblotted onto Immobilon PVDF membrane (Millipore, Bedford, Massachusetts). Internal amino acid sequencing was performed on tryptic peptides of muKS1 and huKS1 by the Protein Sequencing Unit at the University of Auckland, New Zealand.

The determined amino acid sequences for muKS1 and huKS1 are given in SEQ ID NOS: 397 and 398, respectively. These amino acid sequences confirmed that the determined sequences are identical to those established on the basis of the cDNA sequences. The size discrepancy has previously been reported for other chemokines (Richmond A, Balentien E, Thomas HG, Flaggs G, Barton DE, Spiess J, Bordoni R, Francke U, Derynck R, "Molecular characterization and chromosomal mapping of melanoma growth stimulatory activity, a growth factor structurally related to beta-thromboglobulin," *EMBO J.* 7:2025-2033, 1988; Liao F, Rabin RL, Yannelli JR, Koniaris LG, Vanguri P, Farber JM, "Human Nig chemokine: biochemical and functional characterization," *J. Exp. Med.* 182:1301-1314, 1995). The isoelectric focusing point of these proteins was predicted to be 10.26 using DNASIS (HITACHI Software Engineering, San Francisco, California). Recombinant Fc tagged KS1 expresssed and purified using protein A affinity column chromatography revealed a homogenous protein with a molecular mass of 42kDa.

Oxidative burst assay

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Oxidative burst assays were used to determine responding cell types. 1×10^7 PBMC cells were resuspended in 5 ml HBSS, 20mM HEPES, 0.5% BSA and incubated for 30 minutes at 37°C with 5 μ l 5 mM dichloro-dihydrofluorescein diacetate (H₂DCFDA, Molecular Probes, Eugene, Oregon). 2×10^5 H₂DCFDA-labeled cells were loaded in each well of a flat-bottomed 96 well plate. 10μ l of each agonist was added simultaneously into the well of the flat-bottomed plate to give final concentrations of 100 ng/ml (fMLP was used at 10μ M). The plate was then read on a Victor² 1420

multilabel counter (Wallac, Turku, Finland) with a 485 nm excitation wavelength and 535 nm emission wavelength. Relative fluorescence was measured at 5 minute intervals over 60 minutes.

A pronounced respiratory burst was identified in PBMC with a 2.5 fold difference between control treated cells (TR1) and cells treated with 100 ng/ml muKS1 (Fig. 8). Human stromal derived factor- 1α (SDF1 α) (100 ng/ml) and 10 μ M formyl-Met-Leu-Phe (fMLP) were used as positive controls.

Chemotaxis assay

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Cell migration in response to muKS1 was tested using a 48 well Boyden's chamber (Neuro Probe Inc., Cabin John, Maryland) as described in the manufacturer's protocol. In brief, agonists were diluted in HBSS, 20mM HEPES, 0.5% BSA and added to the bottom wells of the chemotactic chamber. THP-1 cells were re-suspended in the same buffer at 3 x 10⁵ cells per 50 µ1. Top and bottom wells were separated by a PVP-free polycarbonate filter with a 5 µm pore size for monocytes or 3 µm pore size for lymphocytes. Cells were added to the top well and the chamber incubated for 2 hours for monocytes and 4 hours for lymphocytes in a 5% CO₂ humidified incubator at 37°C. After incubation, the filter was fixed and cells scraped from the upper surface. The filter was then stained with Diff-Quick (Dade International Inc., Miami, Florida) and the number of migrating cells counted in five randomly selected high power fields. The results are expressed as a migration index (the number of test migrated cells divided by the number of control migrated cells).

Using this assay, muKS1 was tested against T cells and THP-1 cells. MuKS1 induced a titrateable chemotactic effect on THP-1 cells from 0.01 ng/ml to 100 ng/ml (Fig. 9). Human SDF1α was used as a positive control and gave an equivalent migration. MuKS1 was also tested against IL-2 activated T cells. However, no migration was evidence for muKS1 even at high concentrations, whereas SDF-1α provided an obvious titrateable chemotactic stimulus. Therefore, muKS1 appears to be chemotactic for THP-1 cells but not for IL-2 activated T cells at the concentrations tested.

Flow cytometric binding studies

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Binding of KLF-1 to THP-1 and Jurkat cells was tested in the following manner. THP-1 or Jurkat cells (5 x 10⁶) were resuspended in 3 mls of wash buffer (2% FBS and 0.2% sodium azide in PBS) and pelleted at 4°C, 200 x g for 5 minutes. Cells were then blocked with 0.5% mouse and goat sera for 30 minutes on ice. Cells were washed, pelleted, resuspended in 50 µl of KLF-1Fc at 10 µg/ml and incubated for 30 minutes on ice. After incubation, the cells were prepared as before and resuspended in 50 µl of goat anti-human IgG biotin (Southern Biotechnology Associates, AL) at 10 µg/ml and incuated for 30 minutes on ice. Finally, cells were washed, pelleted and resuspended in 50 μl of streptavidin-RPE (Southern Biotechnology Associates, AL) at 10 μg/ml and incuabated for a further 30 minutes on ice in the dark. Cells were washed and resuspended in 250 µl of wash buffer and stained with 1µl of 10 µg/ml propidium iodide (Sigma) to exclude any dead cells. Purified Fc fragment (10 µg/ml) was used as a negative control in place of KLF-1Fc to determine non-specific binding. Ten thousand gated events were analyzed on log scale using PE filter arrangement with peak transmittance at 575 nm and bandwidth of 10 nm on an Elite cell sorter (Coulter Cytometry).

The respiratory burst and migration assays indicated that KS1 is active on monocytes and not T cells; therefore, the KS1 Fc fusion protein was tested in a binding study with THP-1 and Jurkat T cells. KS1 Fc showed a marked positive shift on THP-1 cells compared with the Fc fragment alone. In contrast, KS1 demonstrated no positive binding with Jurkat cells in an identical experiment.

25 Full length sequence of muKS1 clone

The nucleotide sequence of muKS1 was extended by determining the base sequence of additional ESTs. Combination of all the ESTs identified the full-length muKS1 (SEQ ID NO: 370) and the corresponding translated polypeptide sequence in SEQ ID NO: 394.

Analysis of human RNA transcripts by Northern blotting

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Northern blot analysis to determine the size and distribution of mRNA for the human homologue of muKS1 was performed by probing human tissue blots (Clontech, Palo Alto, California) with a radioactively labeled probe consisting of nucleotides 1 to 288 of huKS1 (SEQ ID NO: 270). Prehybridization, hybridization, washing, and probe labeling were performed as described in Sambrook, et al., Ibid. mRNA for huKS1 was 1.6 kb in size and was observed to be most abundance in kidney, liver, colon, small intestine, and spleen. Expression could also be detected in pancreas, skeletal muscle, placenta, brain, heart, prostate, and thymus. No detectable signal was found in lung, ovary, and testis.

Analysis of human RNA transcripts in tumor tissue by Northern blotting

Northern blot analysis to determine distribution of huKS1 in cancer tissue was performed as described previously by probing tumor panel blots (Invitrogen, Carlsbad, California). These blots make a direct comparison between normal and tumor tissue. MRNA was observed in normal uterine and cervical tissue but not in the respective tumor tissue. In contrast, expression was up-regulated in breast tumor and down-regulated in normal breast tissue. No detectable signal was found in either ovary or ovarian tumors.

Injection of bacterially recombinant muKS1 into C3H/HeJ mice

Eighteen C3H/HeJ mice were divided into 3 groups and injected intraperitoneally with muKS1, GV14B, or phosphate buffered saline (PBS). GV14B is a bacterially expressed recombinant protein used as a negative control. Group 1 mice were injected with 50 μg of muKS1 in 1 ml of PBS; Group 2 mice were injected with 50 μg of GV14B in 1 ml of PBS; and Group 3 mice with 1 ml of PBS. After 18 hours, the cells in the peritoneal cavity of the mice were isolated by intraperitoneal lavage with 2 x 4 ml washes with harvest solution (0.02% EDTA in PBS). Viable cells were counted from individual

mice from each group. Mice injected with 50 µg of muKS1 had on average a 3-fold increase in cell numbers (Fig. 10).

20 µg of bacterial recombinant muKS1 was injected subcutaneously into the left hind foot of three C3H/HeJ mice. The same volume of PBS was injected into the same site on the right-hand side of the same animal. After 18 hours, mice were examined for inflammation. All mice showed a red swelling in the foot pad injected with bacterially recombinant KS1. From histology, sites injected with muKS1 had an inflammatory response of a mixed phenotype with mononuclear and polymorphonuclear cells present.

10 Injection of bacterially expressed muKSla into nude mice

To determine whether T cells are required for the inflammatory response, the experiment was repeated using nude mice. Two nude mice were anaesthetised intraperitoneally with 75 µl of 1/10 dilution of Hypnorm (Janssen Pharmaceuticals, Buckinghamshire, England) in phosphate buffered saline. 20ug of bacterially expressed muKS1a (SEQ ID NO: 345) was injected subcutaneously in the left hind foot, ear and left-hand side of the back. The same volume of phosphate buffered saline was injected in the same sites but on the right-hand side of the same animal. Mice were left for 18 hours and then examined for inflammation. Both mice showed a red swelling in the ear and foot sites injected with the bacterially expressed protein. No obvious inflammation could be identified in either back site. Mice were culled and biopsies taken from the ear, back and foot sites and fixed in 3.7% formol saline. Biopsies were embedded, sectioned and stained with Haemotoxylin and eosin. Sites injected with muKS1a had a marked increase in polymorphonuclear granulocytes, whereas sites injected with phosphate buffered saline had a low background infiltrate of polymorphonuclear granulocytes.

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Discussion

Chemokines are a large superfamily of highly basic secreted proteins with a broad number of functions (Baggiolini, et al., Annu. Rev. Immunol., 15:675-705, 1997; Ward, et al., Immunity, 9:1-11, 1998; Horuk, Nature, 393:524-525, 1998). The polypeptide

sequences of muKS1 and huKS1 have similarity to CXC chemokines, suggesting that this protein will act like other CXC chemokines. The in vivo data from nude mice supports this hypothesis. This chemokine-like protein may therefore be expected to stimulate leukocyte, epithelial, stromal, and neuronal cell migration; promote angiogenesis and vascular development; promote neuronal patterning, hemopoietic stem cell mobilization, keratinocyte and epithelial stem cell patterning and development, activation and proliferation of leukocytes; and promotion of migration in wound healing events. It has recently been shown that receptors to chemokines act as co-receptors for HIV-1 infection of CD4+ cells (Cairns, et al., Nature Medicine, 4:563-568, 1998) and that high circulating levels of chemokines can render a degree of immunity to those exposed to the HIV virus (Zagury, et al., Proc. Natl. Acad. Sci. USA 95:3857-3861, 1998). This novel gene and its encoded protein may thus be usefully employed as regulators of epithelial, lymphoid, myeloid, stromal, and neuronal cells migration and cancers; as agents for the treatment of cancers, neuro-degenerative diseases, inflammatory autoimmune diseases such as psoriasis, asthma and Crohn's disease for use in wound healing; and as agents for the prevention of HIV-1 binding and infection of leukocytes.

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We have also shown that muKS1 promotes a quantifiable increase in cell numbers in the peritoneal cavity of C3H/HeJ mice injected with muKS1. Furthermore, we have shown that muKS1 induces an oxidative burst in human peripheral blood mononuclear cells and migration in the human monocyte leukemia cell line, THP-1, suggesting that monocyte/macrophages are one of the responsive cell types for KS1. In addition to this, we demonstrated that huKS1 was expressed at high levels in a number of non-lymphoid tissues, such as the colon and small intestine, and in breast tumors. It was also expressed in normal uterine and cervical tissue, but was completely down-regulated in their respective tumors. It has recently been shown that non-ELR chemokines have demonstrated angiostatic properties. IP-10 and Mig, two non-ELR chemokines, have previously been shown to be up-regulated during regression of tumors (Tannenbaum CS, Tubbs R, Armstrong D, Finke JH, Bukowski RM, Hamilton TA, "The CXC Chemokines IP-10 and Mig are necessary for IL-12-mediated regression of the mouse RENCA

tumor," J. Immunol. 161: 927-932, 1998), with levels of expression inversely correlating with tumor size (Kanegane C, Sgadari C, Kanegane H, Teruya-Feldstine J, Yao O, Gupta G, Farber JM, Liao F, Liu L, Tosato G, "Contribution of the CXC Chemokines IP-10 and Mig to the antitumor effects of IL-12," J. Leuko. Biol. 64: 384-392, 1998). Furthermore, neutralizing antibodies to IP-10 and Mig would reduce the anti-tumor effect, indicating the contribution these molecules make to the anti-tumor effects. Therefore, it is expected that in the case of cervical and uterine tumors, KS1 would have similar properties.

The data demonstrates that KS1 is involved in cell migration showing that one of the responsive cell types is monocyte/macrophage. The human expression data in conjunction with the *in vitro* and *in vivo* biology demonstrates that this molecule may be a useful regulator in cell migration, and as an agent for the treatment of inflammatory diseases, such as Crohn's disease, ulcerative colitis, and rheumatoid arthritis; and cancers, such as cervical adenocarcinoma, uterine leiomyoma, and breast invasive ductal carcinoma.

Example 6

CHARACTERIZATION OF KS2

KS2 contains a transmembrane domain and may function as either a membrane-bound ligand or a receptor. Northern analysis indicated that the mRNA for KS2 was expressed in the mouse keratinocyte cell line, Pam212, consistent with the cDNA being identified in mouse keratinocytes.

Mammalian Expression

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To express KS2, the extracellular domain was fused to the amino terminus of the constant domain of immunoglobulinG (Fc) that had a C-terminal 6xHistidine tag. This was performed by cloning polynucleotides 20-664 of KS2 (SEQ ID NO: 273), encoding amino acids 1-215 of polypeptide KS2 (SEQ ID NO: 347), into the mammalian expression vector pcDNA3 (Invitrogen, NV Leek, Netherlands), to the amino terminus of

the constant domain of immunoglobulinG (Fc) that had a C-terminal 6xHistidine tag. This construct was transformed into competent XL1-Blue *E. coli* as described in Sambrook et al., *Ibid*. The Fc fusion construct of KS2a was expressed by transfecting Cos-1 cells in 5 x T175 flasks with 180 µg of KS1a using DEAE-dextran. The supernatant was harvested after seven days and passed over a Ni-NTA column. Bound KS2a was eluted from the column and dialysed against PBS.

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The ability of the Fc fusion polypeptide of KS2a to inhibit the IL-2 induced growth of concanavalin A stimulated murine splenocytes was determined as follows. A single cell suspension was prepared from the spleens of BALB/c mice and washed into DMEM (GIBCO-BRL) supplemented with 2 mM L-glutamine, 1 mM sodium pyruvate, 0.77 mM L-asparagine, 0.2 mM L-arganine, 160 mM penicillin G, 70 mM dihydrostreptomycin sulfate, 5 x 10⁻² mM beta mercaptoethanol and 5% FCS (cDMEM). Splenocytes (4 x 10⁶/ml) were stimulated with 2 μg/ml concanavalin A for 24 hrs at 37°C in 10% CO₂. The cells were harvested from the culture, washed 3 times in cDMEM and resuspended in cDMEM supplemented with 10 ng/ml rhuIL-2 at 1 x 10⁵ cells/ml. The assay was performed in 96 well round bottomed plates in 0.2 ml cDMEM. The Fc fusion polypeptide of KS2a, PBS, LPS and BSA were titrated into the plates and 1 x 10⁴ activated T cells (0.1 ml) were added to each well. The plates were incubated for 2 days in an atmosphere containing 10% CO₂ at 37°C. The degree of proliferation was determined by pulsing the cells with 0.25 uCi/ml tritiated thymidine for the final 4 hrs of culture after which the cells were harvested onto glass fiber filtermats and the degree of thymidine incorporation determined by standard liquid scintillation techniques. As shown in Fig. 6, the Fc fusion polypeptide of KS2a was found to inhibit the IL-2 induced growth of concanavalin A stimulated murine splenocytes, whereas the negative controls PBS, BSA and LPS did not.

This data demonstrates that KS2 is expressed in skin keratinocytes and inhibits the growth of cytokine induced splenocytes. This indicates a role for KS2 in the regulation of skin inflammation and malignancy.

Example 7

Characterization of KS3

KS3 encodes a polypeptide of 40 amino acids (SEQ ID NO: 129). KS3 contains a signal sequence of 23 amino acids that would result in a mature polypeptide of 17 amino acids (SEQ ID NO: 348; referred to as KS3a).

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KS3a was prepared synthetically (Chiron Technologies, Victoria, Australia) and observed to enhance transferrin-induced growth of the rat intestinal epithelial cells IEC-18 cells. The assay was performed in 96 well flat-bottomed plates in 0.1 ml DMEM (GIBCO-BRL Life Technologies) supplemented with 0.2% FCS. KS3a (SEQ ID NO: 348), apo-Transferrin, media and PBS-BSA were titrated either alone, with 750 ng/ml Apo-transferrin or with 750 ng/ml BSA, into the plates and 1 x10³ IEC-18 cells were added to each well. The plates were incubated for 5 days at 37°C in an atmosphere containing 10% CO₂. The degree of cell growth was determined by MTT dye reduction as described previously (*J. Imm. Meth.* 93:157-165, 1986). As shown in Fig. 7, KS3a plus Apo-transferrin was found to enhance transferrin-induced growth of IEC-18 cells, whereas KS3a alone or PBS-BSA did not, indicating that KS3a and Apo-transferrin act synergistically to induce the growth of IEC-18 cells.

This data indicates that KS3 is epithelial derived and stimulates the growth of epithelial cells of the intestine. This suggests a role for KS3 in wound healing, protection from radiation- or drug-induced intestinal disease, and integrity of the epithelium of the intestine.

SEQ ID NOS: 1-725 are set out in the attached Sequence Listing. The codes for polynucleotide and polypeptide sequences used in the attached Sequence Listing confirm to WIPO Standard ST.25 (1988), Appendix 2.

All references cited herein, including patent references and non-patent references, are hereby incorporated by reference in their entireties.

Although the present invention has been described in terms of specific embodiments, changes and modifications can be carried out without departing from the

scope of the invention which is intended to be limited only by the scope of the appended claims.

We claim:

- 1. An isolated polynucleotide comprising a nucleotide sequence selected from the group consisting of: (a) sequences recited in SEQ ID NOS: 466-487, 510, 511 and 514-623; (b) complements of the sequences recited in SEQ ID NOS: 466-487, 510, 511 and 514-623; (c) reverse complements of the sequences recited in SEQ ID NOS: 466-487, 510, 511 and 514-623; (d) reverse sequences of the sequences recited in SEQ ID NOS: 466-487, 510, 511 and 514-623; (e) sequences having at least a 99% probability of being the same as a sequence selected from any of the sequences in (a)-(d), above, as measured by the computer algorithm BLASTP using the running parameters described above; (f) nucleotide sequences having at least 75% identity to any of the sequences in (a)-(d), above, as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; (g) nucleotide sequences having at least 90% identity to any of the sequences in (a)-(d), above, as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; (h) nucleotide sequences having at least 95% identity to any of the sequences in (a)-(d), above, as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; and (g) open reading frames of SEQ ID NOS: 1-119, 198-276, 349-372, 399-405, 410-412, 416, 418-455, 464, 466-487, 510, 511 and 514-623.
 - 2. An expression vector comprising an isolated polynucleotide of claim 1.
 - 3. A host cell transformed with an expression vector of claim 2.
- 4. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of: (a) sequences provided in SEQ ID NOS: 488-509, 512, 513 and 624-725; (b) sequences having at least a 99% probability of being the same as a sequence of SEQ ID NOS: 488-509, 512, 513 and 624-725, as measured by the computer algorithm BLASTP using the running parameters described above; (c) sequences having

at least 75% identity to a sequence provided in SEQ ID NOS: 488-509, 512, 513 and 624-725, as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; (d) sequences having at least 90% identity to a sequence provided in SEQ ID NOS: 488-509, 512, 513 and 624-725, as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; (e) sequences having at least 95% identity to a sequence provided in SEQ ID NOS: 488-509, 512, 513 and 624-725, as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; and (f) sequences encoded by a sequence provided in SEQ ID NOS: 488-509, 512, 513 and 624-725.

- 5. An isolated polynucleotide encoding a polypeptide of claim 4.
- 6. An expression vector comprising an isolated polynucleotide of claim 5.
- 7. A host cell transformed with an expression vector of claim 6.
- 8. An isolated polypeptide comprising at least a functional portion of a polypeptide having an amino acid sequence selected from the group consisting of: (a) sequences provided in SEQ ID NOS: 196, 488-509, 512, 513 and 624-725; (b) sequences having at least a 99% probability of being the same as a sequence of SEQ ID NOS: 196, 488-509, 512, 513 and 624-725, as measured by the computer algorithm BLASTP using the running parameters described above; (c) sequences having at least 75% identity to a sequence provided in SEQ ID NOS: 196, 488-509, 512, 513 and 624-725, as measured by the computer algorithm BLASTP, using the running parameters and identity test defined above; (d) sequences having at least 90% identity to a sequence provided in SEQ ID NOS: 196, 488-509, 512, 513 and 624-725, as measured by the computer algorithm BLASTP, using the running parameters and identity test defined above; (e) sequences having at least 95% identity to a sequence provided in SEQ ID

NOS: 196, 488-509, 512, 513 and 624-725, as measured by the computer algorithm BLASTP, using the running parameters and identity test defined above; and (f) sequences encoded by a sequence provided in SEQ ID NOS: 466-487, 510, 511 and 514-623.

- A method for stimulating keratinocyte growth and motility in a patient, comprising administering to the patient a composition comprising a polypeptide of claim
- 10. The method of claim 9, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: (a) SEQ ID NOS: 187, 196, 342, 343, 395, 397 and 398; (b) sequences having at least about 50% identity to a sequence of SEQ ID NOS: 187, 196, 342, 343, 395, 397 and 398 as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; (c) sequences having at least about 75% identity to a sequence of SEQ ID NOS: 187, 196, 342, 343, 395, 397 and 398 as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; (d) sequences having at least about 90% identity to a sequence of SEQ ID NOS: 187, 196, 342, 343, 395, 397 and 398 as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; and (e) sequences comprising amino acids 54-104 of SEQ ID NO: 196.
- 11. A method for inhibiting the growth of cancer cells in a patient, comprising administering to the patient a composition comprising a polypeptide of claim 4.
- 12. The method of claim 11, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: (a) SEQ ID NOS: 187, 196, 342, 343, 397 and 398; (b) sequences having at least 75% identity to a sequence of SEQ ID NOS: 187, 196, 342, 343, 397 and 398, as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; (c) sequences having at least 90%

identity to a sequence of SEQ ID NOS: 187, 196, 342, 343, 397 and 398, as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; (d) sequences having at least 95% identity to a sequence of SEQ ID NOS: 187, 196, 342, 343, 397 and 398, as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; and (e) sequences comprising amino acids 54-104 of SEQ ID NO: 196.

- 13. A method for modulating angiogenesis in a patient, comprising administering to the patient a composition comprising a polypeptide of claim 4.
- 14. The method of claim 13, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: (a) SEQ ID NOS: 187, 196, 342, 343, 397 and 398; (b) sequences having at least 75% identity to a sequence of SEQ ID NOS: 187, 196, 342, 343, 397 and 398 as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; (c) sequences having at least 90% identity to a sequence of SEQ ID NOS: 187, 196, 342, 343, 397 and 398 as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; (d) sequences having at least 95% identity to a sequence of SEQ ID NOS: 187, 196, 342, 343, 397 and 398 as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; and (e) sequences comprising amino acids 54-104 of SEQ ID NO: 196..
- 15. A method for inhibiting angiogenesis and vascularization of tumors in a patient, comprising administering to a patient a composition comprising a polypeptide of claim 4.
- 16. The method of claim 15, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: (a) SEQ ID NOS: 187, 196, 342, 343, 397 and 398; (b) sequences having at least 75% identity to a sequence of SEQ ID NOS:

187, 196, 340, 342-346, 397 and 398, as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; (c) sequences having at least 90% identity to a sequence of SEQ ID NOS: 187, 196, 340, 342-346, 397 and 398, as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; (d) sequences having at least 95% identity to a sequence of SEQ ID NOS: 187, 196, 340, 342-346, 397 and 398, as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; and (e) sequences comprising amino acids 54-104 of SEQ ID NO: 196.

- 17. A method for modulating skin inflammation in a patient, comprising administering to the patient a composition comprising a polypeptide of claim 4.
- 18. The method of claim 17, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: (a) SEQ ID NOS: 338 and 347; and (b) sequences having at least 75% identity to a sequence of SEQ ID NOS: 338 and 347 as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; (c) sequences having at least 90% identity to a sequence of SEQ ID NOS: 338 and 347 as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; and (d) sequences having at least 95% identity to a sequence of SEQ ID NOS: 338 and 347 as measured by the computer algorithm BLASTP using the running parameters and identity test defined above.
- 19. A method for stimulating the growth of epithelial cells in a patient, comprising administering to the patient a composition comprising a polypeptide of claim 4.
- 20. The method of claim 19, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: (a) SEQ ID NOS: 129 and 348; (b) sequences having at least 75% identity to a sequence of SEQ ID NOS: 129 and 348 as measured by the computer algorithm BLASTP using the running parameters and identity

test defined above; (c) sequences having at least 90% identity to a sequence of SEQ ID NOS: 129 and 348 as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; and (d) sequences having at least 95% identity to a sequence of SEQ ID NOS: 129 and 348 as measured by the computer algorithm BLASTP using the running parameters and identity test defined above.

- 21. A method for inhibiting the binding of HIV-1 to leukocytes in a patient, comprising administering to the patient a composition comprising a polypeptide of claim 4.
- 22. The method of claim 21, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: (a) SEQ ID NOS: 340, 344, 345, 346 and 465; (b) sequences having at least 75% identity to a sequence of SEQ ID NOS: 340, 344, 345, 346 and 465 as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; (c) sequences having at least 90% identity to a sequence of SEQ ID NOS: 340, 344, 345, 346 and 465 as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; and (d) sequences having at least 95% identity to a sequence of SEQ ID NOS: 340, 344, 345, 346 and 465 as measured by the computer algorithm BLASTP using the running parameters and identity test defined above.
- 23. A method for treating an inflammatory disease in a patient, comprising administering to the patient a composition comprising a polypeptide of claim 4.
- 24. The method of claim 23, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: (a) SEQ ID NOS: 340, 344, 345, 346 and 465; (b) sequences having at least 75% identity to a sequence of SEQ ID NOS: 340, 344, 345, 346 and 465 as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; (c) sequences having at least 90%

identity to a sequence of SEQ ID NOS: 340, 344, 345, 346 and 465 as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; and (d) sequences having at least 95% identity to a sequence of SEQ ID NOS: 340, 344, 345, 346 and 465 as measured by the computer algorithm BLASTP using the running parameters and identity test defined above.

- 25. A method for treating cancer in a patient, comprising administering to the patient a composition comprising a polypeptide of claim 4.
- 26. The method of claim 25, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: (a) SEQ ID NOS: 340, 344, 345, 346 and 465; (b) sequences having at least 75% identity to a sequence of SEQ ID NOS: 340, 344, 345, 346 and 465 as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; (c) sequences having at least 90% identity to a sequence of SEQ ID NOS: 340, 344, 345, 346 and 465 as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; and (d) sequences having at least 95% identity to a sequence of SEQ ID NOS: 340, 344, 345, 346 and 465 as measured by the computer algorithm BLASTP using the running parameters and identity test defined above.
- 27. A method for treating a neurological disease in a patient, comprising administering to the patient a composition comprising a polypeptide of claim 4.
- 28. The method of claim 27, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of: (a) SEQ ID NOS: 187, 196, 340, 342-346, 397 and 398; (b) sequences having at least 75% identity to a sequence of SEQ ID NOS: 187, 196, 340, 342-346, 397 and 398, as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; (c) sequences having at least 90% identity to a sequence of SEQ ID NOS: 187, 196, 340, 342-346, 397

and 398, as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; (d) sequences having at least 95% identity to a sequence of SEQ ID NOS: 187, 196, 340, 342-346, 397 and 398, as measured by the computer algorithm BLASTP using the running parameters and identity test defined above; and (e) sequences comprising amino acids 54-104 of SEQ ID NO: 196.

SEQUENCE LISTING

<110> Watson, James D. Strachan, Lorna Sleeman, Matthew Onrust, Rene Murison, James G. Kumble, Krishanand D. <120> Compositions isolated from skin cells and methods for their use <130> 11000.1011c4U <160> 725 <170> FastSEO for Windows Version 3.0 <210> 1 <211> 696 <212> DNA <213> Rat <400> 1 aattcggcac gaggccgagg cgggcaggca ccagccagag cagctggcgg cagacagtcg gaccgagaca gttggaccga gacagtcgaa cggtctaaca gggcctggct tgcctacctg 120 geagetgeae ceggteettt teecagaget ggttetgtgg gteaacatgg teecetgett cctcctgtct ctgctgctac ttgtgaggcc tgcgcctgtg gtggcctact ctgtgtccct 240 cccggcctcc ttcctggagg aagtggcggg cagtgggggaa gctgagggtt cttcagcctc 300 ttccccaagc ctgctgccgc cccggactcc agccttcagt cccacaccag ggaggaccca 360 gcccacaget ccggtcggcc ctgtgccacc caccaacctc ctggatggga tcgtggactt 420 cttccgccag tatgtgatgc tcattgcggt ggtgggctcg ctgacctttc tcatcatgtt 480 catagtotgo goggoactoa toacgogoca gaagcacaag gocacageot actaccogto 540 ctctttcccc gaaaagaagt atgtggacca gagagaccgg gctggggggc cccatgcctt 600 cagogaggto cotgacaggg cacotgacag coggoaggaa gagggootgg acttottoca 660 geageteeag getgacatte tggettgeta eteaga 696 <210> 2 <211> 475 <212> DNA <213> Rat <400> 2 cggtatcgat aagcttgata tcgaattcct gcaggtcgac actagtggat ccaaagaatt cggcacgaga aaataaccaa ccaaacaaac tttcctcttc ccgctagaaa aaacaaattc 120 tttaaggatg gagctgctct actggtgttt gctgtgcctc ctgttaccac tcacctccag 180 gacccagaag ctgcccacca gagatgagga actttttcag atgcagatcc gggataaggc 240 attgtttcac gattcatccg tgattccaga tggagctgaa atcagcagtt acctatttag 300 agatacacct agaaggtatt tetteatggt tgaggaagat aacaccccac tgteagteac 360 agtgacacct tgtgatgcgc ctttggaatg gaagcttagc ctccaggagc tgcctgagga 420

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cgtcactcct gtgttctggc ctcttgagtg cctttggagg tgtctctgac ctgtgaggat
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cagagacagt ccccgttttt aaacttcgac aattgacttt tatttccttt tctaattttt
                                                                      660
attattttt aaaacaacca ggatgattat cacatctact cccccatccg tccagaaaag
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ccccaaattg attecttcag ggtctggcct gcccaggctc tattccacat gtgcaggttc
                                                                      780
caacagetta accetattet etteccagte atetgetgea ggtatagetg teteatgece
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     <211> 1359
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<212> DNA
      <213> mouse
      <220>
      <221> unsure
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gaacgcaaga gtccttatgt cgccatatgc tgtatagtga tggccttcag catcctcttc
atacagtage tttggaaact accagcatgt gettgetate agactgtaaa caaggacttg
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cctccagaaa ataatgggaa gaatggttaa gccatttgtc tctgaacatg gaatgagata
                                                                      360
aacttcaaga tgctgttctc tatttttatg ctattggacc aatgagctga atgaataatt
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aagatgtaac agttcaatac acaggaatgt gattgtatcc atcaacctca gttctctcac
                                                                       480
tecagtatta cattetgeaa atgteattet gttgtgteag gaetgetttt cataaggtte
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aataatgtct tcacagaatg gtacctctag cgactgtcct attnttattg agaaaaaaac
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agtattttaa acaaaactct gaatttcttt agttagccta agagttggct tctagtcaca
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tgtagtcttg tcttccaaat agaacgtcca tcgtagttac ccaaaggtgg tatttgtggt
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gttcttaatg cagtgcttta agtctagtgt atgttctgtc agcttgaact ggaatctctc
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                                                                     1140
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                                                                     1200
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qaattaaatc ctagctgaaa actatacata gcatttatta attaattact gggtttaact
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gctcttttta aaagtttgaa aaaaaaaaa aaaactcg
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      <210> 35
      <211> 797
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catctggtgg ggaacacage geeggggete ggagaceatg gegggegetg eggtgaagta
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cttaagtcag gaggaggctc aggccgtgga ccaagagctt tttaacgagt atcagttcag
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cgtggatcaa ctcatggagc tggccgggtt gagctgtgcc acggctattg ccaaggctta
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tecececacy tetatgteca agagtecece gaetgtettg gteatetgtg geeeeggaaa
                                                                       360
taacggaggg gatgggctgg tctgtgcgcg acacctcaaa ctttttggtt accagccaac
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tatctattac cccaaaagac ctaacaagcc cctcttcact gggctagtga ctcagtgtca
                                                                       480
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gaaaatggac atteetttee ttggtgaaat geecceagag gatgggatgt agagaaggga
aaccctagcg gaatccaacc agacttactc atctcactga cggcacccaa gaagtctgca
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                                                                       660
actcacttta ctggccgata tcattacctt gggggtcgct ttgtaccacc tgctctagag
aagaagtacc agctgaacct gccatcttac cctgacacag agtgtgtcta ccgtctacag
                                                                       720
taagggaggt gggtaggcag gatteteaat aaagaettgg taetttetgt ettgaaaaaa
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aaaaaaaaa aaactcg
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      <210> 36
      <211> 896
      <212> DNA
      <213> mouse
```

```
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cccatcccag atttgcttag tttgtctccc aatgtgctgg actttaaaga cagggaatgg
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agaagcagat ggatgcttca gtttcagtca tttttggctc tatagtgatc tctgccttcc
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tgtacctgtc cttggctgga ccctgggcag taactgtcac tcagatgagg acgatcatca
                                                                     300
ttacaatgga ccaactgagg gatgccctca tattagacca attaaaagtt gctgtgagtt
                                                                     360
aaaccaggaa tgaccgcact tccacatcag aaatcaaaca aaatcaatgg ttgaagaaca
                                                                     420
tggttaggag cctggctagg tatctttgag agatggatgc agctggctac tcaggcaggt
                                                                     480
aagcaatgga ggtcagccac accctatcgt gatgcactcc ccatgttcag ggtaactgaa
                                                                     540
gaagtgggta aggccagctg aaggccagtc agggcaactt agatgtagcc tggcttctac
                                                                     600
ttccagcctc cggggacagg caaacacatt ttgggaagta agatgatgtc ccaattatta
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tcagtttttt gatatcacag tattgtcaca gggagcactg ggggtccagg ctagcctggg
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atgitactig gittaatgaa ggccccctca accccaacag cccctcctgc tcagggacac
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agtteteace caattacaca ttaataacae acaaacagtg cetageaatg ggecag
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                                                                     120
cagcatcgtt cttatatgcg actaacagaa aaggaagatg aatcattacc aatagatata
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gttcttcaga cacttctggc ctttgcagtt acctgttatg gcatagttca tatcgcaggg
                                                                     240
gagttcaaag acatggatgc cacttcagaa ttaaagaata agacatttga taccttaagg
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gcaacaaatt cttcaaacct agatgcattg tcctctaata catcgttgaa gttacgaaag
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tttgactcac tgcgccgtta agctttttac aaattaaata acaggacaga cacagaattg
                                                                     480
agtattggag tttggggtgt a
                                                                     501
     <210> 38
     <211> 766
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     <213> mouse
     <400> 38 ·
                                                                     60 -
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cgggcggcat cccccggccg ccgcacgcac aggccggcgc cctccttgcc tccctgctcc
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ccaccgcgcc cctccggcca gcatgaggct cctggcggcc gcgctgctcc tgctgctcct
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                                                                     300
gatccgctac agcgacgtga agaagctgga aatgaagcca aagtacccac actgcgagga
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600
ataagacaaa ttatatattg ctatgaagct cttcttacca gggtcagttt ttacatttta
                                                                     660
                                                                     720
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     <211> 480
     <212> DNA
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<213> mouse

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180
aatcattctc acatgcttcc atgtttgttt ctgagaggtg ggggctcaaa tgtataqaaa
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gtaggcccca gtccataagg aggtgtgaac acacccctt actgcttatc acccatttga
                                                                   300
caggaacgcc caggagggga gggggagggg aagaggtgag ttctgcacag tcggacattt
                                                                   360
ctgttgcttt tgcatgttta atatagacgt tcctgtcgat ccttgggaga tcatggcctt
                                                                   420
cagatatgca cacgaccttt gaattgtgcc tactaattat agcaggggac ttgggtaccc
                                                                   480
     <210> 40
      <211> 962
     <212> DNA
      <213> mouse
     <400> 40
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cattcatctc teteteatte ecctgetetg catectgatg agaaactgtt tggettttaa
                                                                   120
aaatgatgcc acagaaatcc tttattcaca tgtggttaaa cctgtcccgg cacaccccag
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cagcaacagc accetgaatc aagccaggaa tggaggcagg catttcagta gcactggact
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ggatcgaaac agtcgagttc aagtgggctg cagggaactg cggtccacca aatacatttc
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ggacggccag tgcaccagca tcagccctct gaaggagetg gtgtgcgegg gcgagtgctt
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gcccctgccg gtgcttccca actggatcgg aggaggctac ggaacaaagt actggagccg
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                                                                   600
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gagetagace tggaetgact aggaageate tgetaceeag atttgattge ttggaagaet
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ctctctcgag cctgccattg ctctttcctc acttgaaagt atatgctttc tgctttgatc
                                                                   780
aagcccagca ggctgtcctt ctctgggact agcttttcct ttgcaagtgt ctcaagatgt
                                                                   840
aatgagtggt ttgcagtgaa agccaggcat cctgtagttt ccatcccctc ccccatccca
                                                                   900
960
                                                                   962
aa
     <210> 41
     <211> 794
     <212> DNA
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ggtggggaac acagegeegg ggeteggaga ccatggeggg egetgeggtg aagtaettaa
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gaggggatgg gctggtctgt gcgcgacacc tcaaactttt tggttaccag ccaactatct
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attaccccaa aagacctaac aagcccctct tcactgggct agtgactcag tgtcagaaaa
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tagoggaato caaccagact tactcatoto actgacggca cocaagaagt otgoaactca
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ctttactggc cgatatcatt accttggggg tcgctttgta ccacctgctc tagagaagaa
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gtaccagetg aacctgccat cttaccetga cacagagtgt gtctaccgtc tacagtaagg
                                                                   720
gaggtgggta ggcaggattc tcaataaaga cttggtactt tctgtcttga aaaaaaaaa
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aaaaaaaact cgag
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<210> 42
      <211> 1152
      <212> DNA
      <213> mouse
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                                                                     120
tetgtgacta tagggaggtt agcacttttt ctaattggaa ttettetetg teetgtggee
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ccatccctca cccgctcttg gcctggacca gatacatgca gcctctttct ccagcacagc
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ctttccctga gcctgaggtt agggcagagt ttagagggtg ggctaagtgt atgtttcat
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gtatgcattc atgcctgtga gtgtgtggct tgctgtcgtg tcctctggga tcccaagcca
                                                                     360
cgcgggtctt ccctctgtag atgggtcctg ggttctatca cctgcttatt tatgtacgag
                                                                     420
gttgggggt ggacccaggg tgggttgatt gtctctttgt aaggaagtat gtgtcggggg
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tgacacgagg ctaagcccga gaaaccccgg gagacagcac tgcataagaa actggtttcc
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600
aaacaaaaca aaaataactc tgaagggcgg gaggataccc aagcctgatg cctgagagga
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gtccctagac ttcagcaact ccgctgcgtg gcctgagccc agcgggaggg atggggagag
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teteagecta geaceacetg teecegagte tteteagett geecateatt eteggegee
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gcctgcccag cc
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ccaggtcctc tggagaaata accagtgctc ttaaccacta agccatctca acagccccaa
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ctaatataga ttatttatga attcaggtgg cttaatggta tatgcatgaa ttagtagtaa
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aacaagaact agggccagca agtggcttaa gggtgcctgc taaccatctc agccacctga
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gttcagtctc caggaaccac acagtg
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                                                                     120
acacagagac agatgccgtg agctccagaa gtaatggacg gcccccact gctggcgctg
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gagatggggc tcctgggagc tcaggcgatg agcccccatc gtcctcctcc caagacgagg
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agttgctgat gcctcctgat ggcctcacgg acacagactt ccagtcatgc gaggacagcc
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<210> 45

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gcccacaget ccggtcggcc ctgtgccacc caccaacetc ctggatggga tcgtggactt
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                                                                       420
ctctttcccc gaaaagaagt atgtggacca gagagaccgg gctggggggc cccatgcctt
                                                                       480
cagcgaggtc cctgacaggg cacctgacag ccggcaggaa gagggcctgg acttcttcca
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      <210> 46
      <211> 306
      <212> DNA
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cttcgtagcc ctggggtgga ttttcctcct cttccacaga gatgcttttt ctctgcatac
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catgtetget ggttteccaa aateteegge aaacecacae caccetecae tgaggeteag
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ccccag
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      <211> 439
      <212> DNA ·
      <213> mouse
      <400> 47
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gcacatatta ctgagccatt gcaagcaatg ggaggggtcc acaatgacac acacacaca
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acacacaca atacacatac acacacccc gagacagtgc cagagctaac agcctacatg
                                                                       240
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tgtattttgg ccaaacttgg aaaataggtt tccttcttcg ttttgcttcc agccttttat
ttgcaagtga tcttccatgc agtatgaaac atgcagacag cactggagtg tggcaagagt
                                                                       360
                                                                       420
gagettgeec cacaagtete teggggatgt tgtactettg tgtgtgttta cagtateatg
                                                                       439
gctgttacat ctactggtc
                                                                         . . 2.
      <210> 48
      <211> 159
      <212> DNA
      <213> mouse
      <220>
      <221> unsure
      <222> (3)...(3)
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ctetttetet tittetgtit cttgtteece titteecetti teetggtgag aaageacata
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                                                                       159
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```

```
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                                                                       360
gaggggtga getecegete egeteggatt tetteggace tteteaggaa catagtgeet
                                                                       420
                                                                       465
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      <211> 337
      <212> DNA
      <213> Rat
      <220>
                                                                        60 -
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tecattetge tgtggtaatt tagnatgtee eetteacaga gaaagatttt nagaacggee
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ctcagaacat atacaacctg tacgagcaag tcagctacaa ctgtttcatc gccgcgggcc
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tctacctcct cctcgggggc ttctccttct gcnaagttcg tctcaataag cgcaaggaat
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      <213> Rat
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aagcetgeet egetgeeage ettgeeetag egetaaatgg tgtetttace aacateataa
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tgcccattct t
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                                                                      180
aattattgag gggactaggc tatatgcatt tgccttcatc cacccatgtt tattaagaat
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cattgtgctt aataatacca agactaagca ccataaccaa gaaatactaa tgtaaagatt
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aacaagatca cagetteeta tgaggaccgg gtgacettet tgecaactgg tateacette
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     <212> DNA
      <213> Human
      <400> 55
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      <213> Human
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      <212> DNA
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                                                                       190
gcgtattcgg
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      <211> 413
      <212> DNA
      <213> mouse
      <400> 58
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aggggtcgac accagagatg ctccaagggc ctgcaccaag ttgcttttgg gttttttctg
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                                                                       360
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      <213> mouse
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      <222> (223)...(223)
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21

<210> 63

<211> 399

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      <213> Rat ·
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caaaaaaaa a
                                                                      2411
      <210> 76
      <211> 1335
      <212> DNA
      <213> mouse
      <400> 76
                                                                        60
acccaaacag cccgggacca tgctgtcgct ccgctccttg cttccacacc tgggactgtt
cetqtqcctq getetgcact tatecccete cetetetgcc agtgataatq ggteetgcgt
                                                                       120
ggtccttgat aacatctaca cctccgacat cttggaaatc agcactatgg ctaacgtctc
                                                                       180
                                                                       240
tggtggggat gtaacctata cagtgacggt ccccgtgaac gattcagtca gtgccgtgat
octgaaagca gtgaaggagg acgacagccc agtgggcacc tggagtggaa catatgagaa
                                                                       300
                                                                       360
gtgcaacgac agcagtgtct actataactt gacatcccaa agccagtcgg tcttccagac
                                                                       420
aaactggaca gttcctactt ccgaggatgt gactaaagtc aacctgcagg tcctcatcgt
                                                                       480
cgtcaatcgc acagcctcaa agtcatccgt gaaaatggaa caagtacaac cctcagcctc
aaccectatt cetgagagtt etgagaccag ceagaccata aacacgacte caactgtgaa
                                                                       540
cacagccaag actacagcca aggacacagc caacaccaca geegtgacca cagccaatac
                                                                       600<sub>6</sub>
                                                                       660
cacagecaat accacagecg tgaccacage caagaccaca gecaaaagec tggccateeg
cactetegge agececetgg caggtgeect ceatatectg ettgttttte teattagtaa
                                                                       720
                                                                       780
actcctctty taaagaaaac tggggaagca gatctccaac ctccaggtca tcctcccgag
                                                                       840
ctcatttcag gccagtgctt aaacataccc gaatgaaggt tttatgtcct cagtccgcag
                                                                       900
ctccaccacc ttggaccaca gacctgcaac actagtgcac ttgagggata caaatgcttg
cotggatett teagggeaca aatteegett ettgtaaata ettagteeat eeateetgeg
                                                                       960
tgtaacctga agttctgact ctcagtttaa cctgttgaca gccaatctga acttgtgttt
                                                                      1020
cttgccaaag gtattcccat gagcctcctg ggtgtggggg tggggaggga atgatccttc
                                                                      1080
tttactttca aactgatttc agatttctgg ccaaacctac tcaggttgca aaggacttat
                                                                      1140
                                                                      1200
gtgacttatg tgactgtagg aaaaagagaa atgagtgatc atcctgtggc tactagcaga
tttccactgt gcccagacca gtcggtaggt tttgaaggaa gtatatgaaa actgtgcctc
                                                                      1260
agaagccaat gacaggacac atgacttttt ttttctaagt caaataaaca atatattgaa
                                                                      1320
                                                                      1335
caaggaaaaa aaaaa
```

```
<210> 77
      <211> 440
      <212> DNA
      <213> mouse
      <220>
      <221> misc_feature
      <222> (1)...(440) `
      <223> n = A,T,C or_G
cactagggnc tecaaagaat teageacgag gagaageett geecaeteaa atacetggge
                                                                    60
catcagctgc accggctcca ctcccatctg ctccaggccc tgaagagaag ccaacacttt
                                                                   120
traggeret caaceterar atragaarag gragageetg tggtgtrage tgttgatera
                                                                   180
aaggcaaccc ttggtggggt tggggttgta aagtagtgat gctaatttct aagcaacaag
                                                                   240
ctctgagctg cagcccccag gccctccagg gcagtccagg gcagtgccag ggttcagggt
                                                                   300
agttctaggg gtctagtatc tggatcaaca agtcccagag ttgggcccag tggctgctga
                                                                   360
cttgttcaat gaccaagaat atacgaccta accttttta tttggttggg caaccacagc
                                                                   420
                                                                   440
tccgagtaag tcatcaaggc
      <210> 78
      <211> 204
       <212> DNA
       <213> mouse
      <400> 78
 ctccataaaa ttcctcaaaa tctgttcccc cagcagattt cctgtgccat cttgggctcc
                                                                    120
 cttcctattc tttcccgtct ttagggcctc ctcacagtgt tgttttctaa caacgcaggc
 180
                                                                    204
 cctctgtgtc ctcttcatcc caat
       <210> 79
       <211> 300
       <212> DNA
       <213> mouse
     · <220>
      <
       <400> 79
tatttatgac ttgggttaag ggagtttgct gtgcaatcat gaagaccaga gttcagatcc
                                                                   ·60
cagcacccat atagcaagag agcatacaag aagcacctgt gactgcactc tgaagaatcc
                                                                   120
aacaccttct tctggcctcc atggcacaca gaacccccca acacatgctc atccactctc
                                                                   240
aaagagacat acataaaaat aaatatttag gtcctgggtc cctcagagac tagtcttcac
aggtcctaaa tacaaacgna gcggaccgca aagggtgagg gagtggncct gaagaagcta
                                                                   300
       <210> 80
       <211> 214
       <212> DNA
       <213> mouse
 cccagaccct gtgtcagcta tcccagcaga aaaagaagat gcggaccctc tcagcaagtc
                                                                     60
 aggtgaggaa acccaggaag cagggtcatg accccgcaga ggtcgggggct cctggtgcag
                                                                    120
 aggatcagat cttgtgtgac ttctgtcttg gggccagcag agtaagggca gtgaaatcct
                                                                    180
 gtctgacctg catggtgaaa tactgtaagg agca
```

```
<210> 81
      <211> 152
      <212> DNA
      <213> mouse
      <220>
      <400> 81
ccccttaact aacccaggac cttccactaa gtggaaggct ccaccatcca cagaggggc
cagtcatttt taagcacacg gaccttttgt gagacagtcg tgatcttaac tgtggtgtca
                                                                      120
ctgatggagc tgaacggtat cccctaaaag ta
                                                                      152
      <210> 82
      <211> 181
      <212> DNA
      <213> mouse
      <220>
     <400> 82
teteagtgat gatgagaage teeggaggag geaggagaaa geagggeece geeceteect
gggtctccac ccacccacgc ccgctaaggt cacctgttct cccatggaga tgatgaagaa
                                                                      120
getcataget ggacaaggee eggaacetea geceagtaac egacetaett eeegeetggg
                                                                      180
                                                                      181
      <210> 83
      <211> 332
      <212> DNA
      <213> mouse
      <220>
     <400> 83
tatagagatg gtgatgtaat gggccagggt gtaagettca acctggggga ttttgctggt
                                                                       60
tttgttgttt ccctgtgtag ccctaacaag cctgtgtaga ccaggctggc tttaactttg
                                                                      120
cagatgacat tcacgtctac ttctctctgt gttggggtta tgggtctgca cacctgccca
                                                                      180
ggcctaggct gggggatttt gaagtatctt agattatgga gtagacccag agtttgcaag
                                                                      240 -
tatctgcttt aaagtgacac ataaacatag cctcctgacc atcttccaca gtgggaccct
                                                                      300
gatctggcct ctccctggaa gaagagagaa ag
                                                                      332
      <210> 84
     <211> 213
      <212> DNA
      <213> mouse
     <400> 84
gcaggcagat aacaatgatt actggacaga gtgcttcaac gcattggaac aggggaggca
                                                                       60
atatgtggat aatcccacag gcgggaaagt ggacgaggct ctggtgagaa gtgccaccgt
                                                                      120
acattgttgg ccgcacagca acgtgctgga cacaagcatg ctctcatccc cagatgtggt
                                                                      180
gegeatgetg etgteeetge agecetteet gea
                                                                      213
      <210> 85
```

<211> 273

```
<212> DNA
       <213> mouse
       <220>
       <221> misc_feature
       <222> (1)...(273)
       <223> n = A,T,C or G
       <400> 85
ceggetetet eteteeteet teecegeete ttetgeetee eetgeetgga aetetgatga
                                                                       60
ggagggacca ggtggtcagg caccccagtc tgatcaggac tcctgtggcc tccagagttt
                                                                      120
canteceeg tecatectga agegggetee tegggagegt ceaggteang tggeetttaa
                                                                      180
eggeateane gtetactatt teccaeggtg ceaaggatte accagtgtge ceaageegtg
                                                                      240
gtggctgtac cctgggnatg gcttctcggc aca
                                                                      273
       <210> 86
       <211> 218
       <212> DNA
       <213> mouse
       <400> 86
 ctcagccgcc tgctctgggg gctggagggt ctcccactta actgtgtctg ccgttcaggg
 ggctcaccca gtgctgcgct acacagaggt tttccctcca gctccagtcc gtcctgccta
                                                                       120
 ctccttctat aaccgcctcc aagagctggc ctcactgttg ccccggccgg ataagccctg
                                                                        180
 cccagcctat gtggagccta tgactgtggt ttgtcacc
                                                                       218
       <210> 87
       <211> 335
       <212> DNA
       <213> mouse
       <400> 87
 gaggtggggt gggtgcatag cctgcctgca attgctgccg ctgggcttaa cgtgttgtga
                                                                        60
 gctggccggt ttcctacaca gcagcacctg ccatggagcc tggccacaag gccactcaga
                                                                       120
 gctgggtgga cagagtgtga ccagaaactc cctgtgggtt ctgataaagg attctcccat
                                                                       180
 aggcaaggtt cagagaacct gggcctcctg ttctcaggga ggcctgtcta tccccagcct
                                                                       240
 ctgagctgtt tcgtcctagt tggtgagtta agtggcatag ccctcttgag gcctctgatg
                                                                       300
 tggaagggc acagaattgc aattattctt gcatg
                                                                       335
       <210> 88
       <211> 410
       <212> DNA
       <213> mouse
       <400> 88
                                                                         60
 aaaccccgcc aggaaacaaa taccggtgta tcggctttac tgaatgcatt tattcccaaa
 gggaaactga aaagcaacct agggacactg taagcagaaa gctgaggctt ttaaaaaaccc
                                                                       120
 accttggcaa tgtaacttgg gaggttccca cacacccagg gctgtgcatc gtgaaattct
                                                                       180
 gtctcctgag acgctgagaa acccttcctt gcagctataa tgggcctggc cgcccagtgt
                                                                       240
 ggagctgtag cttcccacga cgtagccctc aggaacttca ggagggatgc cacagtctat
                                                                       300
 ttctgaaaac aaaaccgtgt caacttcttt actttacaaa tgcaagtttt cagaatccac
                                                                       360
 catctctctg cacccatacc ccatgcctca caccccagac cctgtgttag
       <210> 89
       <211> 279
       <212> DNA
       <213> mouse
```

<220>

```
<400> 89
gtgcagagag tggattgtca gtggactgct Cagttacaaa tgggacatct aacacacaca
                                                                  60
cacacacaca cacacacaca cacacacaca caccccaagg cttagagacc attgcagaag
                                                                 120
agaagagttt atgggaaatc ttggagaaaa cattggatgg tttgagagaa tggttaggag
                                                                 180
240
gacagggtgg agggcattgt ccgacagaac cattgctgt
                                                                 279
     <210> 90
     <211> 398
     <212> DNA
     <213> mouse
     <400> 90
ccaccaaccc agaaatttga caaaggggtt gaatgttgga ctttgcgtcc ttccccggca
                                                                  60
gtggatgtac tgttttgagc cctgtgtgga acttctgaac ttcgtgctgt aactttcaga
actettagac atgggtgtgc tcactgaact ctagggtctg tgtgctagat gctgccaacg
                                                                 180
ctgtattcag gacctgaagt gagtacccgt gtggatccag accaatccag tgtgagacta
                                                                 240
ctgaagaaca tctgttgcca gaacggccac accaaacaga tggagtgccc cagcacttag
                                                                 300
cttcttaaat aacatcggaa ccattcagcc agcgagtctg tgtttgcttt ttgttaaatt
                                                                 360
gtecgecgaa tetaaattee tecaaaagge ttgtgace
                                                                 398
     <210> 91
     <211> 279
     <212> DNA
     <213> mouse
     <400> 91
gttgttactt cagttgctct cggcgggaat tcttaaactg catcctgagt gagggagctt
tggcgagaaa gcaagaccca gtggtagaca gattagcatt actgtacagc ttctttgggt
                                                                 120
                                                                 180
gttcgaggaa gcccggctgg accatagtgg ccacggcggt gaggtaggcg tggacagggc
tqaccagtcc aagttaagga cgttcgggtc catgttaacc ctgccttgta cgtccagcat
                                                                 240
                                                                 279
cgtaagaaaa aacacttgag aacccgaaga ggagatgga
     <210> 92
     <211> 401
     <212> DNA
     <213> mouse .
     <400> 92
aaaaagtttt accaaaacct tttattgact tttataaatt agatagtatt tcaaagttta
                                                                  60
120
cacgetetge aatgaateat gtggcaccga gtetacgeca aggeeeccga gaaaetttat
                                                                 180
tccatagatg ggcagatggt tcccaaagtt acactacaga actacaaatc gactcttaaa
                                                                 240
                                                                 300
attaaaacgg gactttacaa gcattctaga agactcaaac ttgaagcaat ttttggaaaa
taaatgtaca gagaaaagat cttqaagcta ctgaacagag aaccctcatt aaccgagcaa
                                                                 360
                                                                  401
atacatecta tggagettee gaggagtaea cagacagaee g
     <210> 93
      <211> 339
      <212> DNA
     <213> mouse
     <400> 93
```

```
ccactgacct tcccagaagg tgacagccgg cggcggatgt tgtcaaggag ccgagatagt
                                                                        60
                                                                       120
ccagcagtgc ctcggtaccc agaagacggg ctgtctcccc ccaaaagacg gcgacattcg
atgagaagtc accacagtga tctcacattt tgcgagatta tcctgatgga gatggagtcc
                                                                       180
                                                                       240
catgatgcag cctggccttt cctagagcct gtgaaccctc gcttggtgag tggataccga
cgtgtcatca agaaccctat ggatttttcc accatgcgag aacgcctgct ccgtggaggg
                                                                       300
                                                                       339
tacactaget cagaagagtt tgcagetgat getetgetg
      <210> 94
      <211> 55
      <212> DNA
      <213> mouse
      <400> 94
ggggtgtggg caacttggat aacctcagct gettecatet ggetgacate tttgg
                                                                        55
      <210> 95
      <211> 186
      <212> DNA
      <213> mouse
      <400> 95
                                                                        60
qqactctqqc ttcctqqqgc tqcqqccqac ctcqqtqqat cccqctctqa gqcqqcqqcq
gcggggcccc agaaacaaga agcgcggctg gaggaggctc gccgaggagc cgctggggtt
                                                                       120
                                                                       180
agaggtcgac cagttcctgg aagacgtccg gctacaggag cgcacgaccg gtggcttgtt
                                                                       186
ggcaga
      <210> 96
      <211> 244
      <212> DNA
      <213> mouse
      <400> 96
ggtgaccaaa acccettetg ccccettece agagactetg acttgaccet etttecaatt
ccctctcccc aaggccatgg attatgaagc ccctctgtaa gatggtgagc caggggccct
                                                                       1.20
aagagggcat gaggcacacc ctgatcactg tctcaggcct ttgtgggcac tgactcgacc
                                                                        180
                                                                        240
ctggcccacc tcacgcccc aggccagttg gcaactggtg gctcttgagg gctcttacgc
                                                                        244
cctt
       <210> 97
       <211> 116
       <212> DNA
       <213> mouse
       <220>
       <221> unsure
       <222> (11) ... (11)
       <221> unsure
       <222> (13)...(13)
       <221> unsure
       <222> (41)...(41)
 acceggtetg ngnactgeec geettetggg getteettta naggatacag tettttacce
                                                                         60
 atctaggact cctgccaccc tgactgctga cttacagcta tgaggtcccg gcttct
```

```
<210> 98
       <211> 307
       <212> DNA
       <213> mouse
       <400> 98
ccccgggcca tctgtcgcca taccgggccc gtgcaagctt ttgcaggttt tagaagatgg
                                                                         60
cgaattcatg acacetgtga tecaggacaa ceceteagge tggggteeet gtgeegttee
                                                                        120
tgagcaattt cgggatatgc cctaccagcc attcagcaaa ggagatcggc tgggaaaggt
                                                                        180
tqcaqactqq acaqggcca cataccagga caagaggtac acaaacaagt attcctctca
                                                                        240
gttcggtggg gggagtcagt atgcatattt ccatgaggag gatgagacaa gctttccagc
                                                                        300
                                                                        307
tgggtgg
       <210> 99
    . <211> 360
       <212> DNA
       <213> mouse
       <220>
       <221> misc_feature
       <222> (1) ... (360)
       <223> n = A, T, C \text{ or } G
       <400> 99
ccttggtgca ccagetccag cctcaggact tcctcctcct ggccctgaca gcccagetct
tgtcccagca gaatccagtg acaggaagga gtttctgagg caggggagga ggcttctcca
                                                                       120
tgggaaccag acageettge tteactgtat aagtgeeetg atcacaegea gaatgaagtg
                                                                       180
ccaggttgct cagaagcaca aagggtgtgg ctactggccc taaccatgga ctacgtggtt
                                                                       240
                                                                       300
ctaaccaaag actctagaac tctggggtgg gggagaaaca atgtgttctg tgctccagaa
ccttnggctt cctggcccat atggatgggc ttggcaagga acctacctct tctctaaggt
                                                                       360
       <210> 100
       <211> 257
       <212> DNA
       <213> mouse
       <400> 100
                                                                         60
 tgccgcgctg agaggggggg ccgcaccacc agcgccacca ccaccaccgc cgccgccgc
 gggtggggtg ggagggggg gagccaccgc taccgccgcc gcctcccggg tgggcgccct
                                                                         120
                                                                         180
 tctccttaga cgccggcgac ccaggacgag ggcttcatca ctgtaaatgg ttgcaagccg
 acaaagctgc acctcctgaa aaagacggac agcccatcgc gtgagctgta gaaatttgtg
                                                                         240
                                                                        25%
 gacgcatttc tatcggt ·
       <210> 101
       <211> 203
       <212> DNA
       <213> mouse
       <400> 101
 ccaaagtgcc.cattgtgatt caagacgata gccttcccac ggggccccct ccacagatcc
                                                                          60
 gcatcctcaa gaggcccacc agcaacggtg tggtcagcag ccccaactcc accagcaggc
                                                                         120
                                                                         180
 cagcccttcc tgtcaagtcc ctagcacagc gggaggCaga gtatgcagag gctcggagac
                                                                         203
 ggatcctagg cagtgccagc cct
       <210> 102
       <211> 300
```

```
<212> DNA
     <213> mouse
     <400> 102
agtacagaga ceteggetge agettaaace teggacagtg geaacgeece teaateaagt
                                                                        60
                                                                       120
agccaaccc aactcagcca tctttggggg agccaggccc agagaggaag tggttcagaa
ggagcaagaa tgagcttagg ttgggaggga atggggcgtg ggggagctgg agcaagacca
                                                                       180
eggeetggtg geageeggte geeetacagg ecceatteee geetggeact gteeteetta
                                                                       240
cageggaaac acagagettg tgagtgcatg teagetgtta acaagtggtt tetagtacat
                                                                       300
      <210> 103
      <211> 370
      <212> DNA
      <213> mouse
      <220>
     <400> 103
                                                                        60
cagcaactgt ttcaggagct gcacggtgta cgcctgctga ctgatgcgct ggaactaaca
ctgggcgtgg cccccaaaga aaaccctccg gtgatgcttc cagcccaaga gacggagagg
                                                                       120
gccatggaga tcctcaaagt gctctttaat atcacctttg actctgtcaa gagggaagtt
                                                                       180
gatgaggaag atgctgccct ttaccggtac ctggggactc ttctgcggca ctgcgtgatg
                                                                       240
                                                                       300
gttgaagctg ctggggaccg cacagaggag ttccacggcc acacggtgaa tctcctgggg
aacttgcccc tcaagtgttt ggatgtgctt ctggccctgg agctccacga aggatcctta
                                                                       360
                                                                       370
gagtcaatgg
      <210> 104
      <211> 423
      <212> DNA
      <213> mouse
      <400> 104
tttcccagcc tggtggagca gccgactggc gagtgtgcca actgtcccgt gcttcccagc
                                                                        60
tectacettg cetgtettet eteteetggg aagatgttee tggtgggget gaegggagge
                                                                       120
ategeeteag geaagagete egteateeag gtatteeaac agetgggetg tgetgtaate
                                                                       180
                                                                       240
gacgtggacg tcattgcgcg gcacgttgtc cagccagggt atcctgccca ccggcgtata
                                                                       300
gtagaggeet tiggeactga agtetigetg gagaatggeg acategaceg caaggieete
                                                                       360
qqaqacetqa tetteaacea qeetqacegt eggeagetge teaacteeat tacceacect
                                                                       420
gagateegea aggaaatgat gaaggagace tteaagtaet teteegaggt accgataegt
gat
                                                                       423
      <210> 105
      <211> 117
      <212> DNA
      <213> mouse
                                                                        60
agettggtge tgttcatatt taaactgata aagactette ataggagetg agggtageaa
gcccgcgtcg gtgactgggg tctcacacag gttcagcact tggagcatag tgaggtg
                                                                       117
      <210> 106
      <211> 133
      <212> DNA
      <213> mouse
      <400> 106
```

60

```
ttttttttt aaaataccac catttccaat cccaaaagaa catggcactt gtttgtttct
teceettete atteateea gaettteaag tgttttette aataetgagg ettteteetg
                                                                      120
cagetetggt etg
                                                                      133
     <210> 107
     <211> 217
      <212> DNA
      <213> mouse
     <220>
     <221> unsure
     <222> (1)...(1)
     <221> unsure
     <222> (11)...(11)
     <221> unsure
      <222> (18)...(23)
      <221> unsure
     <222> (34)...(34)
     <221> unsure
     <222> (37)...(38)
     <221> unsure
     <222> (40)...(42)
      <221> unsure
     <222> (50)...(52)
      <221> unsure
      <222> (55)...(58)
      <221> unsure
     <222> (152)...(152)
      <221> unsure
     <222> (155)...(155)
     <221> unsure
      <222> (165)...(165)
     <400> 107
ntttttttg ngcgcacnnn nnngnnnncg cccnggnngn nnagcctacn nncannnngt
                                                                      60
tttcttctcc aggctgaaga cctgaacgtc aagttggaag gggagccttc catgcggaaa
                                                                      120
ccaaagcagc ggccgcggcc ggagcccctc ancancccca ccaangeggg cactttcatc
                                                                      180
gcccctcctg tctactccaa catcacccct taccaga
                                                                      217
     <210> 108
      <211> 346
      <212> DNA
     <213> mouse
      <220>
     <400> 108
```

```
gggcatagaa ggcatctcga aaagaatact tatttgaatt gaaggaagat gaagaggcct
gcaggaaggc tcagaagaca ggagtgtttt acctctttca tgacctggat cctttgctcc
                                                                       120
 aggegteagg acategatac etggtgeece ggettageeg ageagagttg gaagggetge
                                                                       180
tgggtaagtt cggacaggat tcgcaaagaa ttgaagattc ggtgctggtt gggtgctccg
                                                                       240
agcagcagga agcatggttt gctttggatc taggtctgaa gagtgcctcc tccagccgtg
                                                                       300
gacaagtatc gctgctccag cagcttgact gctgtaaaga ggatct
                                                                       346
       <210> 109
       <211> 242
       <212> DNA
       <213> mouse
       <400> 109
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ttacaagcta gagggtggcc ggcgagtaac cccgcccaag gggaggattg tccttgatgg
                                                                       120
 ctgcaccatc acctgccct gcctggagta tgaaaaccgg ccgctcctca ttaaactgaa
                                                                       180
                                                                       240
gacccgaact tccactgagt acttcctgga agcctgttct cgagaggaga gagactcctg
                                                                       242
       <210> 110
       <211> 310
       <212> DNA
       <213> mouse
      <220>
       <221> misc_feature
       <222> (1)...(310)
       <223> n = A,T,C or G
       <400> 110
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eggeteecc geggeeegee eteetgeegg cetegeegeg gteteecttg eteeetgaga
                                                                      120
                                                                      180
tegetgageg etgageageg geeegggaga ggaggeettg ggegaegggg egeggagagg
                                                                      240
gagggcgggc gggcantggg ggcgccgcgg atctctatat ggcgacgggt ctgtcgggtc
tggctgtccg gctgtcgcgc tcggccggnc ggccggttcc tatggggtct tctgcaaagg
                                                                      300
                                                                      310
ggttgacccg
       <210> 111
       <211> 228
       <212> DNA
       <213> mouse
       <400> 111
ttctttttta acatttggtg gtttttttct ttactctttt tttcttttcc ttcttttct
                                                                        60
 gccctcaacc ccccaactcc tttggtatga agtactttta acatttatat ttcattgtta
                                                                       120
 cactttaaat tttgtaagga aaactctgat atttcattcc tcctgaacca ctaatgttag
                                                                       180
 aatttatttc taagaatcag tcaacatgta tactcttaat agtgaatt
                                                                       228
       <210> 112
       <211> 292
       <212> DNA
       <213> mouse
       <400> 112
 gtggggtccc agacttgcca accaaagggc cattcctggt atatggttct ggcttcagct
                                                                        60
 ctggtggcat ggactatggt atggttggtg gcaaggaggc tgggaccgag tctcgcttca
                                                                        120
                                                                       180
 aacagtggac ctcaatgatg gaagggctgc catctgtggc cacacaagaa gccaccatgc
```

| | | | | aggttcacca tcctgctggt | | 292 |
|--------------------------|--|--------------------------|--------------------------|--|--------------------------|--------------------------------|
| | | | | | | |
| <220> | • | | | | | |
| <400> | | | | | | 60 |
| caaccagaaa actacaagaa | aagacctcag cagccacgtg gcctaaccga | caatgtatag atcacagttt | acctggaata gagggtggaa | tgaaaacact tatagtgttg ggcaggggtg tcttctactt | ccctggttaa tgactgagtt | 60 120 180 240 255 |
| <211; <212; | > 114 > 197 > DNA > mouse | | | · | | • |
| | > 114 tgaacageeg | cgtgtatgtc | acactgctct | gtgtgtgatt | tcttcacgtg | 60 |
| tgcatgtgcg | ctcttggtct gttttattcc | ttccacttat | tgcctcgttc | gtaagaaacc aatgtacaga | aaccataagg | 120 180 197 |
| <211: <212: | > 115 > 205 > DNA > mouse | | | | • | |
| <400 | > 115 | | | | | |
| aacataggtg gtcatataca | aaaacagcca | aacacataat atatatactt | gtacaatctg | aaaaaaacaa gtgttccagg tatattatga | acaaacatct | 60 120 180 205 |
| | > 116 > 202 | | | • | | , |
| <212 | > DNA > mouse | | | | ě | · co |
| <220 | .• | | | . • | | • |
| | > 116 ' cctctacttc | ccttttcctt | cctgcttgat | tttctcattc | cagaccccta | 60 |
| tgcacacaca | cacacacaca | cacacacaca | cacgaacaca | cgcacacaca | cacacacacg | 120 |
| | | | atttagtttt | ccattcctag | agagatctaa | 180 202 |
| ·tcatccccta | gtcagtgcct | aa | | | | . 202 |
| <211 <212 | > 117 > 240 > DNA > mouse | | | | | |

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ccgccaggag aggagataca cagccagtga tgtggaccac cggatggctg ttgctgctgc
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cgcttctgct gtgtgaagga gcgcaagccc tggagtgcta cagctgcgtg cagaaggcgg
                                                                    120
acgatggatg cgctccgcac aggatgaaga cagtcaaatg tggtcccggg gtggacgtct
                                                                    180
gtaccgagge cgtgggageg gtagagacca tecacgggca attetetgtg geggtgeggg
                                                                    240
     <210> 118
     <211> 527
      <212> DNA
     <213> Human
     <400> 118
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gttccaatat cagtctatct tttattcaac gcaatgacag cactgaccga agaggcagcc
gtgactgtaa cacctccaat cacagcccag caaggtaact ggacagttaa caaaacagaa
                                                                    180
geteacaaca tagaaggace catageettg aagtteteac acetttgeet ggaagateat
                                                                    240
aacagttact gcatcaacgg tgcttgtgca ttccaccatg agctagagaa agccatctgc
                                                                    300
aggtgtttta ctggttatac tggagaaagg tgtgagcact tgactttaac ttcatatgct
                                                                    360
gtggattett atgaaaaata cattgcaatt gggattggtg ttggattact attaagtggt
                                                                    420
tttcttgtta ttttttactg ctatataaga aagaggtgtc taaaattgaa atcgccttac
                                                                    480
                                                                    527
aatgtctgtt ctggagaaag acgaccactg tgaggccttt gtgaaga
      <210> 119
      <211> 655
      <212> DNA
      <213> Rat
      <400> 119
                                                                     60
atggcgcgcc ccgcgccctg gtggtggctg cggccgctgg cggcgctcgc cctggcgctg
gegetggtee gggtgeeete ageeegggee gggcagatge egegeeeege agagegeggg
                                                                    120
                                                                    180
ccccagtac ggctcttcac cgaggaggag ctggcccgct acagcggcga ggaggaggat
caacccatct acttggcagt gaagggagtg gtgttcgatg tcacctctgg gaaggagttt
                                                                    240
tatggacgtg gagcccccta caacgccttg gccgggaagg actcgagcag aggtgtggcc
                                                                    300
aagatgtege tggateetge agaceteact catgacattt etggteteac tgecaaggag
                                                                    360
ctggaagccc tcgatgacat cttcagcaag gtgtacaaag ccaaataccc cattgttggc
                                                                    420
                                                                    480
tacacggccc gcaggatcct caacgaggat ggcagcccca acctggactt caagcctgaa
gaccaqccc attttgacat aaaggacgag ttctaatgtc tagctgagaa gctggttcta
                                                                    540
gggagaggtg aggggacagg agttaaatgt cccacggaac aagcagggga agcctctgag
                                                                    600
655
      <210> 120
      <211> 176
      <212> PRT
      <213> Rat
      <400> 120
Met Val Pro Cys Phe Leu Leu Ser Leu Leu Leu Val Arg Pro Ala
                5
                                  10
                                                      15
Pro Val Val Ala Tyr Ser Val Ser Leu Pro Ala Ser Phe Leu Glu Glu
                               25
            20
                                                  30
Val Ala Gly Ser Gly Glu Ala Glu Gly Ser Ser Ala Ser Ser Pro Ser
       35
                         40
                                            . 45
Leu Leu Pro Pro Arg Thr Pro Ala Phe Ser Pro Thr Pro Gly Arg Thr
                                           60
    50
                       55
Gln Pro Thr Ala Pro Val Gly Pro Val Pro Pro Thr Asn Leu Leu Asp
65
                                .
```

```
Gly Ile Val Asp Phe Phe Arg Gln Tyr Val Met Leu Ile Ala Val Val
             85
                               90
Gly Ser Leu Thr Phe Leu Ile Met Phe Ile Val Cys Ala Ala Leu Ile
                          105
         100
                                           110
Thr Arg Gln Lys His Lys Ala Thr Ala Tyr Tyr Pro Ser Ser Phe Pro
                       120
      115
                                         125
Glu Lys Lys Tyr Val Asp Gln Arg Asp Arg Ala Gly Gly Pro His Ala
                  135
                                   140
  130
Phe Ser Glu Val Pro Asp Arg Ala Pro Asp Ser Arg Gln Glu Glu Gly
              150
                         155
Leu Asp Phe Phe Gln Gln Leu Gln Ala Asp Ile Leu Ala Cys Tyr Ser
                              170
              165
                                               175
     <210> 121
     <211> 116
     <212> PRT
     <213> Rat
     <400> 121
Met Glu Leu Leu Tyr Trp Cys Leu Leu Cys Leu Leu Leu Pro Leu Thr
           5
                         10
Ser Arg Thr Gln Lys Leu Pro Thr Arg Asp Glu Glu Leu Phe Gln Met
        20
                           25
Gln Ile Arg Asp Lys Ala Leu Phe His Asp Ser Ser Val Ile Pro Asp
                     40
     35
                                       45
Gly Ala Glu Ile Ser Ser Tyr Leu Phe Arg Asp Thr Pro Arg Arg Tyr 50 60
                             . 60
                  55
   50
Phe Phe Met Val Glu Glu Asp Asn Thr Pro Leu Ser Val Thr Val Thr
                                75
65 70
Pro Cys Asp Ala Pro Leu Glu Trp Lys Leu Ser Leu Gln Glu Leu Pro
           . 85
                            . 90 ·
                                                95 -
Glu Glu Ser Ser Ala Asp Gly Ser Gly Asp Pro Glu Pro Leu Asp Gln
         100
                           105
Gln Lys Gln Gin
       115
     <210> 122
     <211> 64
     <212> PRT
     <213> Human
     <400> 122
Met Asn Leu Leu Ile Gly Ser Ile Ile Leu Ser Ser Phe Leu Val Leu
1 5
                              10
Ser Asp Gly Asp Thr Thr Ala Ser Pro Ser Ser Met Ser Ser Ser
         20
                            25
                                              30
Val Leu Asn His Ile Ser Ser Ser Ser Ser Val Trp His Leu Phe
                40 45
     35
Asp Ile Cys Asp Ser Ser Lys Trp Asn Ala Tyr Cys Gln Val Trp Gly
   50
                     55
     <210> 123
     <211> 68
     <212> PRT
     <213> Human
     <400> 123
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Met Leu Thr Leu Pro Ile Leu Val Cys Lys Val Gln Asp Ser Asn Arg
Arg Lys Met Leu Pro Thr Gln Phe Leu Phe Leu Gly Val Leu Gly
         20
Ile Phe Gly Leu Thr Phe Ala Phe Ile Ile Gly Leu Asp Gly Ser Thr
                         40'
     35
Gly Pro Thr Arg Phe Phe Leu Phe Gly Ile Leu Phe Ser Ile Cys Phe
                    55`
Ser Cys Leu Leu
     <210> 124
     <211> 110
     <212> PRT
     <213> mouse
     <400> 124
Met Ile Ser Pro Ala Trp Ser Leu Phe Leu Ile Gly Thr Lys Ile Gly
                          10
Leu Phe Phe Gln Val Ala Pro Leu Ser Val Val Ala Lys Ser Cys Pro
          20
                             25
Ser Val Cys Arg Cys Asp Ala Gly Phe Ile Tyr Cys Asn Asp Arg Ser
      35
                         40
                                           45
Leu Thr Ser Ile Pro Val Gly Ile Pro Glu Asp Ala Thr Thr Leu Tyr
                                60
  50
                   55.
Leu Gln Asn Asn Gln Ile Asn Asn Val Gly Ile Pro Ser Asp Leu Lys
                 70 '
                                   75
Asn Leu Leu Lys Val Gln Arg Ile Tyr Leu Tyr His Asn Ser Leu Asp
                          90
             85
Glu Phe Pro Thr Asn Leu Pro Lys Tyr Val Lys Glu Leu His
                             105
          100
     <210> 125
     <211> 330
     <212> PRT
     <213> mouse
     <400> 125
Met Gly Ser Pro Arg Leu Ala Ala Leu Leu Ser Leu Pro Leu Leu
                           10
Leu Ile Gly Leu Ala Val Ser Ala Arg Val Ala Cys Pro Cys Leu Arg
          20
                            25
Ser Trp Thr Ser His Cys Leu Leu Ala Tyr Arg Val Asp Lys Arg Phe
                        40
Ala Gly Leu Gln Trp Gly Trp Phe Pro Leu Leu Val Arg Lys Ser Lys .
                      55
                                        60
   50
Ser Pro Pro Lys Phe Glu Asp Tyr Trp Arg His Arg Thr Pro Ala Ser
                70
                                   75
Phe Gln Arg Lys Leu Leu Gly Ser Pro Ser Leu Ser Glu Glu Ser His
              85
                                90
                                                  95
Arg Ile Ser Ile Pro Ser Ser Ala Ile Ser His Arg Gly Gln Arg Thr
```

100

115

105 Lys Arg Ala Gln Pro Ser Ala Ala Glu Gly Arg Glu His Leu Pro Glu .120

Ala Gly Ser Gln Lys Cys Gly Gly Pro Glu Phe Ser Phe Asp Leu Leu 130 135 140 Pro Glu Val Gln Ala Val Arg Val Thr Ile Pro Ala Gly Pro Lys Ala

110

125

```
150
                                 155
Ser Val Arg Leu Cys Tyr Gln Trp Ala Leu Glu Cys Glu Asp Leu Ser
          165
                     170 · 175
Ser Pro Phe Asp Thr Gln Lys Ile Val Ser Gly Gly His Thr Val Asp
         180 . 185
                                   190
Leu Pro Tyr Glu Phe Leu Leu Pro Cys Met Cys Ile Glu Ala Ser Tyr
                            205
      195 200
Leu Gln Glu Asp Thr Val Arg Arg Lys Lys Cys Pro Phe Gln Ser Trp
  210 . 215
                                    220
Pro Glu Ala Tyr Gly Ser Asp Phe Trp Gln Ser Ile Arg Phe Thr Asp 225 230 235 240
Tyr Ser Gln His Asn Gln Met Val Met Ala Leu Thr Leu Arg Cys Pro
245 250 255
Leu Lys Leu Glu Ala Ser Leu Cys Trp Arg Gln Asp Pro Leu Thr Pro 260 265 270
Cys Glu Thr Leu Pro Asn Ala Thr Ala Gln Glu Ser Glu Gly Trp Tyr
   275 280 285
Ile Leu Glu Asn Val Asp Leu His Pro Gln Leu Cys Phe Lys Phe Ser
 290 295 300
Phe Glu Asn Ser Ser His Val Glu Cys Pro His Gln Ser Gly Ser Leu 305 310 315 320
Pro Ser Trp Thr Val Ser Met Asp Thr Gln
           325·
     <210> 126
     <211> 37
     <212> PRT
     <213> Rat
     <400> 126
Met Leu Trp Val Leu Leu Ser Leu Thr Pro Leu Leu Ser Pro Leu Ile
              5
                             10
                                              15
Phe Phe Pro Val Lys Thr Val Ala Leu Glu Glu Ile Ser Thr Ile Cys
     20
Arg Ala Asp Val Leu
      35
     <210> 127
     <211> 42
     <212> PRT
   <213> mouse
    <400> 127
Met Gly Ser Pro Ile Ser Gly Val Cys Pro Val Leu Pro Gly Gly Leu
           5
                             10
                                               15
Phe Val Ala Leu Gly Trp Ile Phe Leu Leu Phe His Arg Asp Ala Phe
     20
                      25
Ser Leu His Thr Met Ser Ala Gly Phe Pro
     35
                       40
     <210> 128
     <211> 253
     <212> PRT
     <213> mouse
     <400> 128
Met Met Tyr Trp Ile Val Phe Ala Ile Phe Met Ala Ala Glu Thr Phe
```

```
10
Thr Asp Ile Phe Ile Ser Trp Ser Gly Pro Arg Ile Gly Arg Pro Trp
        20 25 30
Gly Trp Glu Gly Pro His His His His Leu Ala Ser Gly Ser His
     35 · 40
                             45
Lys Pro Leu Pro Leu Leu Thr His Arg Phe Pro Phe Tyr Tyr Glu Phe
 50 55
                              60
Lys Met Ala Phe Val Leu Trp Leu Leu Ser Pro Tyr Thr Lys Gly Ala 65 70 75 80
         70
Ser Leu Leu Tyr Arg Lys Phe Val His Pro Ser Leu Ser Arg His Glu
85 90 95
                                     -95
           85
Lys Glu Ile Asp Ala Cys Ile Val Gln Ala Lys Glu Arg Ser Tyr Glu
100 105 110
Thr Met Leu Ser Phe Gly Lys Arg Ser Leu Asn Ile Ala Ala Ser Ala
     115 120
                                      125
Ala Val Gln Ala Ala Thr Lys Ser Gln Gly Ala Leu Ala Gly Arg Leu
 130 135
                                   140
Arg Ser Phe Ser Met Gln Asp Leu Arg Ser Ile Pro Asp Thr Pro Val
145 150 155 160
Pro Thr Tyr Gln Asp Pro Leu Tyr Leu Glu Asp Gln Val Pro Arg Arg
        165 · 170 175
Arg Pro Pro Ile Gly Tyr Arg Pro Gly Gly Leu Gln Gly Ser Asp Thr
                   185
                                 190
         180
Glu Asp Glu Cys Trp Ser Asp Asn Glu Ile Val Pro Gln Pro Pro Val
195 200 205
Arg Pro Arg Glu Lys Pro Leu Gly Arg Ser Gln Ser Leu Arg Val Val 210 215 220
Lys Arg Lys Pro Leu Thr Arg Glu Gly Thr Ser Arg Ser Leu Lys Val
225 230 235 240
Arg Thr Arg Lys Lys Ala Met Pro Ser Asp Met Asp Ser
                    250
            245
     <210> 129
     <211> 40
     <212> PRT
     <213> mouse
    <400> 129
Met Lys Ala Met Ala Leu Ser Leu Gly Ala Ser Pro Val Leu Ala Phe
1 5 10
Leu Leu Ser Gly Tyr Ser Asp Gly Tyr Gln Val Cys Ser Arg Phe Gly
 20 25
                                           30
Ser Lys Val Pro Gln Phe Leu Asn
      35
     <210> 130
     <211> 87
     <212> PRT
     <213> mouse
     <400> 130
Met Ile Ala Val Thr Phe Ala Ile Val Leu Gly Val Ile Ile Tyr Arg
                         10 15
Ile Ser Thr Ala Ala Ala Leu Ala Met Asn Ser Ser Pro Ser Val Arg
                    25 30
       20
Ser Asn Ile Arg Val Thr Val Thr Ala Thr Ala Val Ile Ile Asn Leu
```

40 .

35

45

```
Val Val Ile Ile Leu Leu Asp Glu Val Tyr Gly Cys Ile Ala Arg Trp
                     55
                                        60
Leu Thr Lys Ile Gly Glu Cys His Val Gln Asp Ser Ile Gly Ser Met
                                    75
               70
Gly Leu Gly Gln Gly Gln Pro
             85
     <210> 131
     <211> 70
     <212> PRT
     <213> mouse
     <400> 131
Met Phe Gly Leu Val His Val Cys Thr Cys Val Cys Val Cys
                              10
           . 5
Val Cys Val Cys Val Cys Ile Cys Ser Cys Gly Tyr Val His Val Pro
      20
                             25
Cys Gly Cys Val Cys Leu Trp Gly Pro Glu Val Arg Tyr Leu Pro Leu
                40
                                          45
Ser Leu His Pro Gly Gly Phe Cys Phe Val Leu Phe Cys Phe Gly Pro 50 55 60
Gly Leu Ser Leu Ile Ser
     <210> 132
     <211> 63
     <212> PRT
     <213> mouse
   ` <400> 132
Met Trp Leu Leu Val Ala Leu Thr Leu Ser Val Tyr Ser Leu Val Ala
               5
                                10
Phe Val Thr Gly Met Leu Cys Asp Thr Val Val Ile Lys Met Leu Met
                            25
                                              30
        20
Ser Leu His Lys Ser Ser Lys Leu Asn Pro Arg Ala Lys Cys Gly Gly
                                          45
    35 40
Val Pro Leu Ile Pro Ala Leu Trp Gly Gln Val Gln Val Val Leu
                     55
- 50
     <210> 133
     <211> 39
     <212> PRT
     <213> mouse
     <400> 133
Met Asp Asn Thr Leu Ser Ile Ile Ile Tyr Leu Leu Phe Ile Phe Ala
           5 . 10 . 15
Ile Ser Val Leu Asp Ser Gln Leu Ser Thr Arg Cys Leu Trp Trp Phe
     20
                                               30
Ser Lys Asp Leu Glu Val Thr
      35
     <210> 134
     <211> 90
     <212> PRT
     <213> Rat
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<400> 134
Met Pro Thr Met Trp Pro Leu Leu His Val Leu Trp Leu Ala Leu Val
                               10
Cys Gly Ser Val His Thr Thr Leu Ser Lys Ser Asp Ala Lys Lys Ala
Ala Ser Lys Thr Leu Leu Glu Lys Thr Gln Phe Ser Asp Lys Pro Val
     35
                       40 .
Gln Asp Arg Gly Leu Val Val Thr Asp Ile Lys Ala Glu Asp Val Val
                  55
                                     60
Leu Glu His Arg Ser Tyr Cys Ser Ala Arg Ala Arg Glu Arg Asn Phe 65 70 75 80
Ala Gly Glu Val Leu Gly Ile Cys His Ser
              85
     <210> 135
     <211> 193
     <212> PRT
     <213> Rat
     <400> 135
Met Thr Ser Gly Pro Gly Gly Pro Ala Ala Ala Thr Gly Gly Lys
             5
                              10
Asp Thr His Gln Trp Tyr Val Cys Asn Arg Glu Lys Leu Cys Glu Ser
  20
                          25
                                             30
Leu Gln Ser Val Phe Val Gln Ser Tyr Leu Asp Gln Gly Thr Gln Ile
 35 40
Phe Leu Asn Asn Ser Ile Glu Lys Ser Gly Trp Leu Phe Ile Gln Leu 50 55 60
Tyr His Ser Phe Val Ser Ser Val Phe Thr Leu Phe Met Ser Arg Thr
65 70
                                75
Ser Ile Asn Gly Leu Leu Gly Arg Gly Ser Met Phe Val Phe Ser Pro
             85
                               90
Asp Gln Phe Gln Arg Leu Leu Lys Ile Asn Pro Asp Trp Lys Thr His
        100
                          105
Arg Leu Leu Asp Leu Gly Ala Gly Asp Gly Glu Val Thr Lys Ile Met
115 120 125
Ser Pro His Phe Glu Glu Ile Tyr Ala Thr Glu Leu Ser Glu Thr Met
                 135
. 130
                             140
150
Trp Gln Asn Thr Gly Phe Gln Tyr Asp Val Ile Ser Cys Leu Asn Leu \cdot 165 \, 170 \, 175
Leu Asp Arg Cys Asp Gln Pro Leu Thr Leu Leu Lys Asp Ile Arg Met
                            185
                                             190
Ser
     <210> 136
     <211> 106
     <212> PRT
     <213> Rat
     <400> 136
Met Ala Ala Pro Met Asp Arg Thr His Gly Gly Arg Ala Ala Arg Ala
                            10
                                    ( 15
Leu Arg Arg Ala Leu Ala Leu Ala Ser Leu Ala Gly Leu Leu Leu Ser
```

25

20

```
Gly Leu Ala Gly Ala Leu Pro Thr Leu Gly Pro Gly Trp Arg Arg Gln
      35
                         40
Asn Pro Glu Pro Pro Ala Ser Arg Thr Arg Ser Leu Leu Leu Asp Ala
            55
 50
                                      60
Ala Ser Gly Gln Leu Arg Leu Glu Tyr Gly Phe His Pro Asp Ala Val 65 70 75 80
               70
                                    75
Ala Trp. Ala Asn Leu Thr Asn Ala Ile Arg Glu Thr Gly Trp Ala Tyr
                              90
Leu Asp Leu Gly Thr Asn Gly Ser Tyr Lys
          100
     <210> 137
     <211> 286
     <212> PRT
     <213> Rat
     <400> 137
Met Ala Ala Ala Met Pro Leu Gly Leu Ser Leu Leu Leu Val Leu
                      10
Val Gly Gln Gly Cys Cys Gly Arg Val Glu Gly Pro Arg Asp Ser Leu
                          25
        20
Arg Glu Glu Leu Val Ile Thr Pro Leu Pro Ser Gly Asp Val Ala Ala
      35
                        40
                                           45
Thr Phe Gln Phe Arg Thr Arg Trp Asp Ser Asp Leu Gln Arg Glu Gly
                   55
                                       60
Val Ser His Tyr Arg Leu Phe Pro Lys Ala Leu Gly Gln Leu Ile Ser 65 70 75 80
                                 75
                 70
Lys Tyr Ser Leu Arg Glu Leu His Leu Ser Phe Thr Gln Gly Phe Trp
                    90
           85
Arg Thr Arg Tyr Trp Gly Pro Pro Phe Leu Gln Ala Pro Ser Gly Ala
          100
                           105
                                               110
Glu Leu Trp Val Trp Phe Gln Asp Thr Val Thr Asp Val Asp Lys Ser
                        120
  115
Trp Lys Glu Leu Ser Asn Val Leu Ser Gly Ile Phe Cys Ala Ser Leu
   130
                     135
                                        140
Asn Phe Ile Asp Ser Thr Asn Thr Val Thr Pro Thr Ala Ser Phe Lys
                150
                                   155
Pro Leu Gly Leu Ala Asn Asp Thr Asp His Tyr Phe Leu Arg Tyr Ala
165 170 175
            165
Val Leu Pro Arg Glu Val Val Cys Thr Glu Asn Leu Thr Pro Trp Lys
180 185 190
          180
Lys Leu Leu Pro Cys Ser Ser Lys Ala Gly Leu Ser Val Leu Leu Lys
      195 200
                                         205
Ala Asp Arg Leu Phe His Thr Ser Tyr His Ser Gln Ala Val His Ile
          215
                                      220
Arg Pro Ile Cys Arg Asn Ala His Cys Thr Ser Ile Ser Trp Glu Leu
        230
                           235
Arg Gln Thr Leu Ser Val Val Phe Asp Ala Phe Ile Thr Gly Gln Gly 245 250 255
Lys Lys Glu Ala Cys Pro Leu Ala Ser Gln Ser Leu Val Tyr Val Asp
                           265
                                               270
         260
Ile Thr Gly Tyr Ser Gln Asp Asn Glu Thr Leu Glu Val Ser
       275
                         280
                                  . 285
     <210> 138
     <211> 198
     <212> PRT
```

<213> Rat

<400> 138 Met Thr Val Phe Arg Lys Val Thr Thr Met Ile Ser Trp Met Leu Leu Ala Cys Ala Leu Pro Cys Ala Ala Asp Pro Met Leu Gly Ala Phe Ala 20 25 Arg Arg Asp Phe Gln Lys Gly Gly Pro Gln Leu Val Cys Ser Leu Pro 35 40 45 Gly Pro Gln Gly Pro Pro Gly Pro Pro Gly Ala Pro Gly Ser Ser Gly 55 60 Met Val Gly Arg Met Gly Phe Pro Gly Lys Asp Gly Gln Asp Gly Gln 65 70 75 80 70 · 75 Asp Gly Asp Arg Gly Asp Ser Gly Glu Glu Gly Pro Pro Gly Arg Thr 85 90 Gly Asn Arg Gly Lys Gln Gly Pro Lys Gly Lys Ala Gly Ala Ile Gly 100 105 110 Arg Ala Gly Pro Arg Gly Pro Lys Gly Val Ser Gly Thr Pro Gly Lys 115 120 125 His Gly Ile Pro Gly Lys Lys Gly Pro Lys Gly Lys Lys Gly Glu Pro 130 135 140 Gly Leu Pro Gly Pro Cys Ser Cys Gly Ser Ser Arg Ala Lys Ser Ala 150 155 Phe Ser Val Ala Val Thr Lys Ser Tyr Pro Arg Glu Arg Leu Pro Ile 170 165 175 Lys Phe Asp Lys Ile Leu Met Asn Glu Gly Gly His Tyr Asn Ala Ser 185 180 190 Ser Gly Lys Phe Val Cys 195

<210> 139 <211> 233

<212> PRT

<213> Rat

<400> 139

Met Ala Ser Ala Leu Glu Glu Leu Gln Lys Asp Leu Glu Glu Val Lys 10 Val Leu Leu Glu Lys Ser Thr Arg Lys Arg Leu Arg Asp Thr Leu Thr 20 25 Asn Glu Lys Ser Lys Ile Glu Thr Glu Leu Arg Asn Lys Met Gln Gln 35 40 45 Lys Ser Gln Lys Lys Pro Glu Phe Asp Asn Glu Lys Pro Ala Ala Val 55 Val Ala Pro Leu Thr Thr Gly Tyr Thr Val Lys Ile Ser Asn Tyr Gly 70 75 Trp Asp Gln Ser Asp Lys Phe Val Lys Ile Tyr Ile Thr Leu Thr Gly 85 90 95 Val His Gln Val Pro Ala Glu Asn Val Gln Val His Phe Thr Glu Arg 100 105 110 Ser Phe Asp Leu Leu Val Lys Asn Leu Asn Gly Lys Asn Tyr Ser Met 115. 120 125 Ile Val Asn Asn Leu Leu Lys Pro Ile Ser Val Glu Ser Ser Ser Lys 140 130 135 Lys Val Lys Thr Asp Thr Val Ile Ile Leu Cys Arg Lys Lys Ala Glu 145 150 155 160 Asn Thr Arg Trp Asp Tyr Leu Thr Gln Val Glu Lys Glu Cys Lys Glu

170

```
Lys Glu Lys Pro Ser Tyr Asp Thr Glu Ala Asp Pro Ser Glu Gly Leu 180 . 185 . 190
Met Asn Val Leu Lys Lys Ile Tyr Glu Asp Gly Asp Asp Met Lys
      195 200
                                       205
Arg Thr Ile Asn Lys Ala Trp Val Glu Ser Arg Glu Lys Gln Ala Arg
210 . 215 220
Glu Asp Thr Glu Phe Leu Gln Pro Gly
225
                  230
     <210> 140
     <211> 38
     <212> PRT
     <213> Human
     <400> 140
Met Gly Leu Ala Leu Cys Leu Ala Ser Ala Gly Ile Ser Gly Ser Arg
                            10
                                                  15
Ser Ala Phe Leu Gly Val Pro Arg Pro Arg Pro Thr Leu Ile Lys Leu
      20
                            25
Ile Asp Thr Val Asp Leu
      35
     <210> 141
     <211> 322
     <212> PRT
     <213> mouse
     <400> 141
Met Asp Ala Arg Trp Trp Ala Val Val Leu Ala Thr Leu Pro Ser
                               10
Leu Gly Ala Gly Gly Glu Ser Pro Glu Ala Pro Pro Gln Ser Trp Thr
                   25
     20
Gln Leu Trp Leu Phe Arg Phe Leu Leu Asn Val Ala Gly Tyr Ala Ser 35 40 45
Phe Met Val Pro Gly Tyr Leu Leu Val Gln Tyr Leu Arg Arg Lys Asn
                   55
Tyr Leu Glu Thr Gly Arg Gly Leu Cys Phe Pro Leu Val Lys Ala Cys
                 70
                                 75
Val Phe Gly Asn Glu Pro Lys Ala Pro Asp Glu Val Leu Leu Ala Pro
85 90 95
             85
                            90
Arg Thr Glu Thr Ala Glu Ser Thr Pro Ser Trp Gln Val Leu Lys Leu 100 105 110
Val Phe Cys Ala Ser Gly Leu Gln Val Ser Tyr Leu Thr Trp Gly Ile
      115 . 120 125
Leu Gln Glu Arg Val Met Thr Gly Ser Tyr Gly Ala Thr Ala Thr Ser
                 135. 140 ...
  130
Pro Gly Glu His Phe Thr Asp Ser Gln Phe Leu Val Leu Met Asn Arg
        150· 155
145
Val Leu Ala Leu Val Val Ala Gly Leu Tyr Cys Val Leu Arg Lys Gln
             165 170
Pro Arg His Gly Ala Pro Met Tyr Arg Tyr Ser Phe Ala Ser Leu Ser
                           185
                                    . 190
          180
Asn Val Leu Ser Ser Trp Cys Gln Tyr Glu Ala Leu Lys Phe Val Ser
                                205
      195
                       200
Phe Pro Thr Gln Val Leu Ala Lys Ala Ser Lys Val Ile Pro Val Met
                                      220
    210
                      215 . .
```

Met Met Gly Lys Leu Val Ser Arg Arg Ser Tyr Glu His Trp Glu Tyr 230 235 Leu Thr Ala Gly Leu Ile Ser Ile Gly Val Ser Met Phe Leu Leu Ser 255 245 250 Ser Gly Pro Glu Pro Arg Ser Ser Pro Ala Thr Thr Leu Ser Gly Leu 265 270 260 Val Leu Leu Ala Gly Tyr Ile Ala Phe Asp Ser Phe Thr Ser Asn Trp 275 280 285 Gln Asp Ala Leu Phe Ala Tyr Lys Met Ser Ser Val Gln Met Met Phe 300 290 295 Gly Val Asn Leu Phe Ser Cys Leu Phe Thr Val Gly Ser Leu Leu Glu 315 310 Gln Gly

> <210> 142 <211> 312 <212> PRT <213> mouse

<400> 142 Met Leu Cys Leu Cys Leu Tyr Val Pro Ile Ala Gly Ala Ala Gln Thr 10 5 Glu Phe Gln Tyr Phe Glu Ser Lys Gly Leu Pro Ala Glu Leu Lys Ser 25 20 Ile Phe Lys Leu Ser Val Phe Ile Pro Ser Gln Glu Phe Ser Thr Tyr 35 40 45 Arg Gln Trp Lys Gln Lys Ile Val Gln Ala Gly Asp Lys Asp Leu Asp 50 55 60 Gly Gln Leu Asp Phe Glu Glu Phe Val His Tyr Leu Gln Asp His Glu 65 70 75 Lys Lys Leu Arg Leu Val Phe Lys Ser Leu Asp Lys Lys Asn Asp Gly 85 90 Arg Ile Asp Ala Gln Glu Ile Met Gln Ser Leu Arg Asp Leu Gly Val 105 100 Lys Ile Ser Glu Gln Gln Ala Glu Lys Ile Leu Lys Ser Met Asp Lys 115 120 125 Asn Gly Thr Met Thr Ile Asp Trp Asn Glu Trp Arg Asp Tyr His Leu 135 140 130 Leu His Pro Val Glu Asn Ile Pro Glu Ile Ile Leu Tyr Trp Lys His 150 155 Ser Thr Ile Phe Asp Val Gly Glu Asn Leu Thr Val Pro Asp Glu Phe 165 170 175 Thr Val Glu Glu Arg Gln Thr Gly Met Trp Trp Arg His Leu Val Ala 185 190 180 Gly Gly Gly Ala Gly Ala Val. Ser Arg Thr Cys Thr Ala Pro Leu Asp 200 195 Arg Leu Lys Val Leu Met Gln Val His Ala Ser Arg Ser Asn Asn Met 210 215 220 215 Cys Ile Val Gly Gly Phe Thr Gln Met Ile Arg Glu Gly Gly Ala Lys 225 230 235 240 Ser Leu Trp Arg Gly Asn Gly Ile Asn Val Leu Lys Ile Ala Pro Glu 250 . 255 245 Ser Ala Ile Lys Phe Met Ala Tyr Glu Gln Met Lys Arg Leu Val Gly 260 . 265 270 Ser Asp Gln Glu Thr Leu Arg Ile His Glu Arg Leu Val Ala Gly Ser 285 280 .

```
Leu Ala Gly Ala Ile Ala Gln Ser Ser Ile Tyr Pro Met Glu Val Leu
   290
                      295
Lys Thr Arg Met Ala Leu Arg Lys
                  310
     <210> 143
     <211> 163
     <212> PRT
     <213> Rat
     <400> 143
Met Pro Leu Val Thr Thr Leu Phe Tyr Ala Cys Phe Tyr His Tyr Thr
                                10
                                                   15
Glu Ser Glu Gly Thr Phe Ser Ser Pro Val Asn Leu Lys Lys Thr Phe
                             25
     20
                                                30
Lys Ile Pro Asp Arg Gln Tyr Val Leu Thr Ala Leu Ala Ala Arg Ala
    . 35
                          40
Lys Leu Arg Ala Trp Asn Asp Val Asp Ala Leu Phe Thr Thr Lys Asn
                     55
Trp Leu Gly Tyr Thr Lys Lys Arg Ala Pro Ile Gly Phe His Arg Val
65
                   70
                                     75
Val Glu Ile Leu His Lys Asn Ser Ala Pro Val Gln Ile Leu Gln Glu
              85
                                90
                                                    95
Tyr Val Asn Leu Val Glu Asp Val Asp Thr Lys Leu Asn Leu Ala Thr
          100
                             105
                                                110
Lys Phe Lys Cys His Asp Val Val Ile Asp Thr Cys Arg Asp Leu Lys
      115
                          120
                                             125
Asp Arg Gln Gln Leu Leu Ala Tyr Arg Ser Lys Val Asp Lys Gly Ser
 130
                                       140
                    135
Ala Glu Glu Lys Ile Asp Val Ile Leu Ser Ser Ser Gln Ile Arg
145
                 150
                                     155
Trp Lys Asn
     <210> 144
     <211> 330
     <212> PRT
     <213> Rat
     <400> 144
Met Ala Gly Trp Ala Gly Ala Glu Leu Ser Val Leu Asn Pro Leu Arg
               5 .
                                 10
Ala Leu Trp Leu Leu Ala Ala Ala Phe Leu Leu Ala Leu Leu
          20
                              25
                                                 30
Gln Leu Ala Pro Ala Arg Leu Leu Pro Ser Cys Ala Leu Phe Gln Asp .
       35
                          40
                                             45
Leu Ile Arg Tyr Gly Lys Thr Lys Gln Ser Gly Ser Arg Arg Pro Ala
   50
                                       60
                     55
Val Cys Arg Ala Phe Asp Val Pro Lys Arg Tyr Phe Ser His Phe Tyr
                                     75
65
                  70
                                                      80
Val Val Ser Val Leu Trp Asn Gly Ser Leu Leu Trp Phe Leu Ser Gln
              85
                                 90
Ser Leu Phe Leu Gly Ala Pro Phe Pro Ser Trp Leu Trp Ala Leu Leu
          100
                            105
                                                110
Arg Thr Leu Gly Val Thr Gln Phe Gln Ala Leu Gly Met Glu Ser Lys
                                             125
                          120
```

Ala Ser Arg Ile Gln Ala Gly Glu Leu Ala Leu Ser Thr Phe Leu Val

```
135
Leu Val Phe Leu Trp Val His Ser Leu Arg Arg Leu Phe Glu Cys Phe
                                    155
      150
Tyr Val Ser Val Phe Ser Asn Thr Ala Ile His Val Val Gln Tyr Cys
                                 170
            165
Phe Gly Leu Val Tyr Tyr Val Leu Val Gly Leu Thr Val Leu Ser Gln 180 185 190
Val Pro Met Asn Asp Lys Asn Val Tyr Ala Leu Gly Lys Asn Leu Leu

105 200 205
Leu Gln Ala Arg Trp Phe His Ile Leu Gly Met Met Met Phe Phe Trp
 210
                  215
                                     220
Ser Ser Ala His Gln Tyr Lys Cys His Val Ile Leu Ser Asn Leu Arg
225 230 235 240
225 230 235 240
Arg Asn Lys Lys Gly Val Val Ile His Cys Gln His Arg Ile Pro Phe
245 250 255
Gly Asp Trp Phe Glu Tyr Val Ser Ser Ala Asn Tyr Leu Ala Glu Leu
          260
                             265
                                               270
Met Ile Tyr Ile Ser Met Ala Val Thr Phe Gly Leu His Asn Val Thr
 275 280
                                   285
Trp Trp Leu Val Val Thr Tyr Val Phe Phe Ser Gln Ala Leu Ser Ala 290 295 300
Phe Phe Asn His Arg Phe Tyr Lys Ser Thr Phe Val Ser Tyr Pro Lys
305 310 315
His Arg Lys Ala Phe Leu Pro Phe Leu Phe
       325
                                  330
     <210> 145
     <211> 301
      <212> PRT
      <213> Rat
     <400> 145
Met Leu Val Ala Phe Leu Gly Ala Ser Ala Val Thr Ala Ser Thr Gly
                               10
Leu Leu Trp Lys Lys Ala His Ala Glu Ser Pro Pro Ser Val Asn Ser 20 25 30
Lys Lys Thr Asp Ala Gly Asp Lys Gly Lys Ser Lys Asp Thr Arg Glu
     35
                                            45
                         40
Val Ser Ser His Glu Gly Ser Ala Ala Asp Thr Ala Ala Glu Pro Tyr
                      55
                                        60
Pro Glu Glu Lys Lys Lys Lys Arg Ser Gly Phe Arg Asp Arg Lys Val
65 70 75 80
                  70
                                   75
Met Glu Tyr Glu Asn Arg Ile Arg Ala Tyr Ser Thr Pro Asp Lys Ile
             85 90
Phe Arg Tyr Phe Ala Thr Leu Lys Val Ile Asn Glu Pro Gly Glu Thr
          100
                             105
                                                 110
Glu Val Phe Met Thr Pro Gln Asp Phe Val Arg Ser Ile Thr Pro Asn
                        120
                                    . 125
     115
Glu Lys Gln Pro Glu His Leu Gly Leu Asp Gln Tyr Ile Ile Lys Arg
130 135 140
                      135
Phe Asp Gly Lys Lys Ile Ala Gln Glu Arg Glu Lys Phe Ala Asp Glu
                            · 155
                 150
Gly Ser Ile Phe Tyr Thr Leu Gly Glu Cys Gly Leu Ile Ser Phe Ser
165 170 175
                              170
             165
Asp Tyr Ile Phe Leu Thr Thr Val Leu Ser Thr Pro Gln Arg Asn Phe 180 185 190
```

Glu Ile Ala Phe Lys Met Phe Asp Leu Asn Gly Asp Gly Glu Val Asp

```
195
                        200
Met Glu Glu Phe Glu Gln Val Gln Ser Ile Ile Arg Ser Gln Thr Ser
               215
                                     220
 210
Met Gly Met Arg His Arg Asp Arg Pro Thr Thr Gly Asn Thr Leu Lys
            230
                          235
Ser Gly Leu Cys Ser Ala Leu Thr Thr Tyr Phe Phe Gly Ala Asp Leu 245 250 255
             245
                             250
Lys Gly Lys Leu Thr Ile Lys Asn Phe Leu Glu Phe Gln Arg Lys Leu
         260
                         265
                                     270
Gln Arg Cys Leu Leu Gly Leu Pro Val Trp Glu Gly Ser Pro His Leu
                    280 285
      275
Pro Thr Gly His Trp Leu Arg Glu Leu Trp Ser Leu Leu
                     295
     <210> 146
     <211> 61
     <212> PRT
     <213> Rat
     <400> 146
Met Glu Asn Ile Tyr Tyr Thr Asn Leu Ile Thr Ile Leu Gly Asn Lys
                             10
His Ala Asn Gln Met Glu Leu Asn Leu Gln Ala Leu Ile Leu Ser Pro
                          25
                                            30
     20
Trp Phe Ala Val Cys Ala Pro Pro Gly Phe Ala Arg Asp Gln Ala Val
    35 40
Arg Gly Leu Ala Leu Ala Gly Arg Arg Ile Thr Val Val
    50
     <210> 147
     <211> 105
      <212> PRT
      <213> Rat
     <400> 147
Met Leu Arg Arg Gln Leu Val Trp Trp His Leu Leu Ala Leu Leu Phe
                               10
 1 5
Leu Pro Phe Cys Leu Cys Gln Asp Glu Tyr Met Glu Ser Pro Gln Ala
                            25
                                              30
        20
Gly Gly Leu Pro Pro Asp Cys Ser Lys Cys Cys His Gly Asp Tyr Gly
                                         45
      35
                        40
Phe Arg Gly Tyr Gln Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Ile 50 55 60
Pro Gly Asn His Gly Asn Asn Gly Asn Asn Gly Ala Thr Gly His Glu
                70
                                 75
Gly Ala Lys Gly Glu Lys Gly Asp Lys Gly Asp Leu Gly Pro Arg Gly
                        90 _. 95
             85
 Glu Arg Gly Gln His Gly Pro Lys Gly
           100
      <210> 148
      <211> 210
      <212> PRT
      <213> Rat
      <400> 148
```

Met Leu Gly Ala Thr Ser Leu Ser Trp Pro Trp Val Leu Trp Ala Val

```
Ala Gln Arg Asp Ser Val Asp Ala Ile Gly Met Phe Leu Gly Gly Leu
                              25
           20
                                                 30
Val Ala Thr Ile Phe Leu Asp Ile Ile Tyr Ile Ser Ile Phe Tyr Ser
      35
                          40
Ser Val Ala Val Gly Asp Thr Gly Arg Phe Ser Ala Gly Met Ala Ile
                     55
Phe Ser Leu Leu Leu Gln Ala Leu Leu Leu Leu Pro Arg Leu Pro His
                 70
                                    75
Ala Pro Gly Ser Glu Gly Val Ser Ser Arg Ser Ala Arg Ile Ser Ser
              85
                                90
Asp Leu Leu Arg Asn Ile Val Pro Thr Arg Gln Leu Thr Arg Gln Thr
          100
                             105
                                                110
His Leu Gln Thr Pro Leu Gln Ala Trp Arg Thr Arg Ala Lys Leu Pro
115 120 125
      115
                         120
Pro Gly Gly Thr Glu Ala Val Pro Gly Arg Pro Gly Ala Gln Gln Asp
  130 135
                                     140
Ala Cys His Leu Leu Tyr Trp Thr Tyr Asn Gly Val Ser Ser Ile Pro
                                   155
         150
Cys His Arg Gly Gly Leu Ser His Val Pro Ser Glu Val Pro Ala Glu
165 170 175
Liys Ser Pro Val Leu Ile Leu His Ala Ala Pro Pro Phe Lys Thr Pro
     180 185 190
Val Asn Pro Trp Ala Arg Thr Val Val Gly Phe Phe Pro Ser Ser Pro
                          200
Ser Leu
  210
      <210> 149
      <211> 301
      <212> PRT
      <213> Rat
      <400> 149
Met Leu Val Ala Phe Leu Gly Ala Ser Ala Val Thr Ala Ser Thr Gly
                                  10
Leu Leu Trp Lys Lys Ala His Ala Glu Ser Pro Pro Ser Val Asn Ser
                              25
Lys Lys Thr Asp Ala Gly Asp Lys Gly Lys Ser Lys Asp Thr Arg Glu
                          40
      35
Val Ser Ser His Glu Gly Ser Ala Ala Asp Thr Ala Ala Glu Pro Tyr
                      55
Pro Glu Glu Lys Lys Lys Lys Arg Ser Gly Phe Arg Asp Arg Lys Val
65 70 75 80
Met Glu Tyr Glu Asn Arg Ile Arg Ala Tyr Ser Thr Pro Asp Lys Ile
                                  90
              85
Phe Arg Tyr Phe Ala Thr Leu Lys Val Ile Asn Glu Pro Gly Glu Thr
                             105
          100
Glu Val Phe Met Thr Pro Gln Asp Phe Val Arg Ser Ile Thr Pro Asn
115 120 125
       115
Glu Lys Gln Pro Glu His Leu Gly Leu Asp Gln Tyr Ile Ile Lys Arg
                      135
                                         140
Phe Asp Gly Lys Lys Ile Ala Gln Glu Arg Glu Lys Phe Ala Asp Glu
                  150
                                 155
Gly Ser Ile Phe Tyr Thr Leu Gly Glu Cys Gly Leu Ile Ser Phe Ser
                                 170
               165
```

Asp Tyr Ile Phe Leu Thr Thr Val Leu Ser Thr Pro Gln Arg Asn Phe

185

```
Glu Ile Ala Phe Lys Met Phe Asp Leu Asn Gly Asp Gly Glu Val Asp
                       200
 195
                                            205
Met Glu Glu Phe Glu Gln Val Gln Ser Ile Ile Arg Ser Gln Thr Ser
 210 215
                                       220
Met Gly Met Arg His Arg Asp Arg Fro Thr Thr Gly Asn Thr Leu Lys 225 230 230 235
Ser Gly Leu Cys Ser Ala Leu Thr Thr Tyr Phe Phe Gly Ala Asp Leu
       245 250 255
Lys Gly Lys Leu Thr Ile Lys Asn Phe Leu Glu Phe Gln Arg Lys Leu 260 265 270
Gln Arg Cys Leu Leu Gly Leu Pro Val Trp Glu Gly Ser Pro His Leu 275 280 285
Pro Thr Gly His Trp Leu Arg Glu Leu Trp Ser Leu Leu
                     295
   290
     <210> 150
     <211> 80
     <212> PRT
     <213> Human
     <400> 150
Met Lys Leu Ser Gly Met Phe Leu Leu Leu Ser Leu Ala Leu Phe Cys
1
                                 10
Phe Leu Thr Gly Val Phe Ser Gln Gly Gly Gln Val Asp Cys Gly Glu
  20
                         25
Phe Gln Asp Thr Lys Val Tyr Cys Thr Arg Glu Ser Asn Pro His Cys 35 40 45
 35
                        40
Gly Ser Asp Gly Gln Thr Tyr Gly Asn Lys Cys Ala Phe Cys Lys Ala
                     55
                                       60
Ile Val Lys Ser Gly Gly Lys Ile Ser Leu Lys His Pro Gly Lys Cys
                   70
     <210> 151
     <211> 27
     <212> PRT
     <213> mouse
     <400> 151
Met Leu Lys Ala Ser Leu His Ile Leu Phe Leu Gly Ile Leu Asn Val
            5
                                 10
Pro Ile Val Asp Thr Ser Thr Lys Thr Gly Val
                              25
           20
      <210> 152
      <211> 86
<212> PRT
      <213> mouse
      <400> 152
Met Leu Gln Gly Pro Ala Pro Ser Cys Phe Trp Val Phe Ser Gly Ile
               5
                                 10 ·
Cys Val Phe Trp Asp Phe Ile Phe Ile Phe Phe Asn Val Leu Ser
      20
                         25
                                             30
Leu Gly Asn Arg Glu Ile Ser Ala Lys Asp Phe Ala Asp Gln Pro Ala
35 40 45
Gly Ala Gln Gly Met Trp Gly Ile Trp Gly His Thr Ile Thr Cys Gly
```

```
Leu Ala Pro Gly Ala Lys Pro Cys Ser Leu Lys Arg Glu Gly Pro Asp
               70
Leu Leu Ser Phe Pro Pro
            85
     <210> 153
     <211> 72
     <212> PRT
     <213> mouse
     <400> 153
Met Ser Ala Ile Phe Asn Phe Gln Ser Leu Leu Thr Val Ile Leu Leu
                       10
Leu Ile Cys Thr Cys Ala Tyr Ile Arg Ser Leu Ala Pro Ser Ile Leu
                             25
Asp Arg Asn Lys Thr Gly Leu Leu Gly Ile Phe Trp Lys Cys Ala Arg
      35
                      40
                                           45
Ile Gly Glu Arg Lys Ser Pro Tyr Val Ala Ile Cys Cys Ile Val Met
                                         60
 50 55
Ala Phe Ser Ile Leu Phe Ile Gln
65
                  70
     <210> 154
     <211> 169
     <212> PRT
     <213> mouse
    <400> 154
Met Ser Gly Leu Arg Thr Leu Leu Gly Leu Gly Leu Leu Val Ala Gly
                                 10
Ser Arg Leu Pro Arg Val Ile Ser Gln Gln Ser Val Cys Arg Ala Arg
 20
                          25
Pro Ile Trp Trp Gly Thr Gln Arg Arg Gly Ser Glu Thr Met Ala Gly 35 40 45
Ala Ala Val Lys Tyr Leu Ser Gln Glu Glu Ala Gln Ala Val Asp Gln
                 55
Glu Leu Phe Asn Glu Tyr Gln Phe Ser Val Asp Gln Leu Met Glu Leu
                 70
                                     75
Ala Gly Leu Ser Cys Ala Thr Ala Ile Ala Lys Ala Tyr Pro Pro Thr
             85
                                90
                                                    95
Ser Met Ser Lys Ser Pro Pro Thr Val Leu Val Ile Cys Gly Pro Gly
                                               110
         100
                             105
Asn Asn Gly Gly Asp Gly Leu Val Cys Ala Arg His Leu Lys Leu Phe
    115
                      120
                                           125
Gly Tyr Gln Pro Thr Ile Tyr Tyr Pro Lys Arg Pro Asn Lys Pro Leu 130 135 140 .
Phe Thr Gly Leu Val Thr Gln Cys Gln Lys Met Asp Ile Pro Phe Leu
145 150 155 160
Gly Glu Met Pro Pro Glu Asp Gly Met
     <210> 155
     <211> 61
     <212> PRT
     <213> mouse
```

```
<400> 155
Met Glu Lys Gln Met Asp Ala Ser Val Ser Val Ile Phe Gly Ser Ile
             5
                              10
Val Ile Ser Ala Phe Leu Tyr Leu Ser Leu Ala Gly Pro Trp Ala Val
        20
                           25
                                            30
Thr Val Thr Gln Met Arg Thr Ile Ile Ile Thr Met Asp Gln Leu Arg
     35
                        40
                                          45
Asp Ala Leu Ile Leu Asp Gl'n Leu Lys Val Ala Val Ser
                     55
     <210> 156
     <211> 131
     <212> PRT
     <213> mouse
   <400> 156
Met Ala Pro Ser Leu Trp Lys Gly Leu Val Gly Val Gly Leu Phe Ala
                             10
Leu Ala His Ala Ala Phe Ser Ala Ala Gln His Arg Ser Tyr Met Arg
     20 25
                                            30
Leu Thr Glu Lys Glu Asp Glu Ser Leu Pro Ile Asp Ile Val Leu Gln
                      40
                                           45
     35
Thr Leu Leu Ala Phe Ala Val Thr Cys Tyr Gly Ile Val His Ile Ala
                              60
 50 55
Gly Glu Phe Lys Asp Met Asp Ala Thr Ser Glu Leu Lys Asn Lys Thr 65 70 75 80
Phe Asp Thr Leu Arg Asn His Pro Ser Phe Tyr Val Phe Asn His Arg
                             90
           85
Gly Arg Val Leu Phe Arg Pro Ser Asp Ala Thr Asn Ser Ser Asn Leu
                           105
                                        110
         100
Asp Ala Leu Ser Ser Asn Thr Ser Leu Lys Leu Arg Lys Phe Asp Ser
     115
                        120
Leu Arg Arg
   130
   <210> 157
     <211> 133
     <212> PRT
     <213> mouse
     <400> 157
Met Arg Leu Leu Ala Ala Ala Leu Leu Leu Leu Leu Leu Ala Leu Cys
                                10
              5
Ala Ser Arg Val Asp Gly Ser Lys Cys Lys Cys Ser Arg Lys Gly Pro
20 25 30
Lys Ile Arg Tyr Ser Asp Val Lys Lys Leu Glu Met Lys Pro Lys Tyr 35 40 45.
                      40
Pro His Cys Glu Glu Lys Met Val Ile Val Thr Thr Lys Glu His Val
                55
Gln Gly Thr Gly Ala Arg Ser Thr Ala Cys Thr Leu Ser Cys Arg Ala
                 70
                                   75
Pro Asn Ala Ser Ser Ser Gly Thr Met Pro Gly Thr Arg Ser Ala Gly
                               90
                                      . 95
Ser Thr Lys Asn Arg Val Asp Asp His Gly Lys Lys Asn Ser Arg Pro
                                    110
          100
                            105
Val Glu Arg Leu Gln Gln Arg Thr Leu Gln Ile Lys Ile Lys Ala Leu
```

120 .

```
Ser Phe Ser Gln Ala
   130
     <210> 158
     <211> 78
     <212> PRT
     <213> mouse
     <400> 158
Gly Thr Arg Lys Pro Leu Pro Met Glu Ala His Ser Arg Arg Glu Lys
                                10
Ala Ser Gly Leu Arg Leu Ala Trp His Tyr Glu Cys Ser Gly Val Ser
                                     30
    20 25
Val Trp Trp Met Cys Val Leu Gly Trp Leu Ser Phe Leu Val Phe Leu
                        40
                                           45
     35
Leu Phe Ser Leu Val Cys Ser Phe Pro Ser Pro Ile Asn His Ser His
                     55
                                    60
Met Leu Pro Cys Leu Phe Leu Arg Gly Gly Gly Ser Asn Val
                  70
    <210> 159
     <211> 206
     <212> PRT
     <213> mouse
     <400> 159
Met Leu Pro Pro Ala Ile His Leu Ser Leu Ile Pro Leu Leu Cys Ile
1 5 10 15
Leu Met Arg Asn Cys Leu Ala Phe Lys Asn Asp Ala Thr Glu Ile Leu 20 25 30
Tyr Ser His Val Val Lys Pro Val Pro Ala His Pro Ser Ser Asn Ser
    35 40
                                          45
Thr Leu Asn Gln Ala Arg Asn Gly Gly Arg His Phe Ser Ser Thr Gly 50 55 60
Leu Asp Arg Asn Ser Arg Val Gln Val Gly Cys Arg Glu Leu Arg Ser
65 70
Thr Lys Tyr Ile Ser Asp Gly Gln Cys Thr Ser Ile Ser Pro Leu Lys
85
90
95
             85
                                90
Glu Leu Val Cys Ala Gly Glu Cys Leu Pro Leu Pro Val Leu Pro Asn
100 105 110
          100
Trp Ile Gly Gly Gly Tyr Gly Thr Lys Tyr Trp Ser Arg Arg Ser Ser. 115 120 125
Gln Glu Trp Arg. Cys Val Asn Asp Lys Thr Arg Thr Gln Arg Ile Gln
130 135 140
  130 135
Leu Gln Cys Gln Asp Gly Ser Thr Arg Thr Tyr Lys Ile Thr Val Val 145 150 150 160
Thr Ala Cys Lys Cys Lys Arg Tyr Thr Arg Gln His Asn Glu Ser Ser
165 170 175
His Asn Phe Glu Ser Val Ser Pro Ala Lys Pro Ala Gln His His Arg
     180 185 190
Glu Arg Lys Arg Ala Ser Lys Ser Ser Lys His Ser Leu Ser
                          200
                                           205
      <210> 160
      <211> 169
      <212> PRT
      <213> mouse
```

```
<400> 160
Met Ser Gly Leu Arg Thr Leu Leu Gly Leu Gly Leu Leu Val Ala Gly
             5
Ser Arg Leu Pro Arg Val Ile Ser Gln Gln Ser Val Cys Arg Ala Arg
                          25
        20
Pro Ile Trp Trp Gly Thr Gln Arg Arg Gly Ser Glu Thr Met Ala Gly
     35 ` 40
Ala Ala Val Lys Tyr Leu Ser Gln Glu Glu Ala Gln Ala Val Asp Gln
                                  60
Glu Leu Phe Asn Glu Tyr Gln. Phe Ser Val Asp Gln Leu Met Glu Leu 65 70 75 80
Ala Gly Leu Ser Cys Ala Thr Ala Ile Ala Lys Ala Tyr Pro Pro Thr
           85 90
Ser Met Ser Lys Ser Pro Pro Thr Val Leu Val Ile Cys Gly Pro Gly
                 105
       100
                                    110
Asn Asn Gly Gly Asp Gly Leu Val Cys Ala Arg His Leu Lys Leu Phe
               120
                              125
    115
Gly Tyr Gln Pro Thr Ile Tyr Tyr Pro Lys Arg Pro Asn Lys Pro Leu
                 135 140 .
   130
Phe Thr Gly Leu Val Thr Gln Cys Gln Lys Met Asp Ile Pro Phe Leu
145 150
                               155
Gly Glu Met Pro Pro Glu Asp Gly Met
       165
```

<210> 161 <211> 114 <212> PRT <213> mouse

<400> 161 Met Ser Val Thr Ile Gly Arg Leu Ala Leu Phe Leu Ile Gly Ile Leu 10 Leu Cys Pro Val Ala Pro Ser Leu Thr Arg Ser Trp Pro Gly Pro Asp 20 25 Thr Cys Ser Leu Phe Leu Gln His Ser Leu Ser Leu Ser Leu Arg Leu 35 40 45 Gly Gln Ser Leu Glu Gly Gly Leu Ser Val Cys Phe His Val Cys Ile 50 55 60 His Ala Cys Glu Cys Val Ala Cys Cys Arg Val Leu Trp Asp Pro Lys
65 70 75 80 70 75 · Pro Arg Gly Ser Ser Leu Cys Arg Trp Val Leu Gly Ser Ile Thr Cys 90 85 Leu Phe Met Tyr Glu Val Gly Gly Trp Thr Gln Gly Gly Leu Ile Val 100 105 Ser Leu

<210> 162 <211> 46 <212> PRT <213> mouse

```
25
Glu Leu Glu Thr Met Val Ser Cys Leu Val Asp Val Gly Asn
      35 . 40 . 45
     <210> 163
     <211> 122
     <212> PRT
     <213> mouse
     <400> 163
Met Phe Thr Phe Val Val Leu Val Ile Thr Ile Val Ile Cys Leu Cys 1 5 10 15
His Val Cys Phe Gly His Phe Lys Tyr Leu Ser Ala His Asn Tyr Lys 20 25 30
Ile Glu His Thr Glu Thr Asp Ala Val Ser Ser Arg Ser Asn Gly Arg
     35
                      40
                                      45
Pro Pro Thr Ala Gly Ala Val Pro Lys Ser Ala Lys Tyr Ile Ala Gln
               55
 50
                                  60
Val Leu Gln Asp Ser Glu Gly Asp Gly Asp Gly Asp Gly Ala Pro Gly 65 70 75 80
        70
                              75
Ser Ser Gly Asp Glu Pro Pro Ser Ser Ser Ser Gln Asp Glu Glu Leu
          85 90 95
Leu Met Pro Pro Asp Gly Leu Thr Asp Thr Asp Phe Gln Ser Cys Glu
       100 105
Asp Ser Leu Ile Glu Asn Glu Ile His Gln
    115 120
     <210> 164
     <211> 60
     <212> PRT
     <213> Rat
    <400> 164
Met Ser Phe Val Lys Ile Glu Ala Thr Pro Thr Gln Thr Lys Trp Pro
                    10
1 . 5
                                       15
Phe Ser Val Val Pro Gln Ser Leu Leu Val Thr Val Tyr Ile Cys Tyr
     20
                        25
Ile Phe Leu Val Ile Phe Phe Phe Phe Phe Glu Ala Cys Gln Glu Val
    35
                   40
Leu Cys Ser Phe Phe Asp Phe Ser Arg Arg Gly
   50
                   55
    <210> 165
     <211> 57
     <212> PRT
     <213> mouse
    <400> 165
Met Gly Ser Pro Ile Ser Gly Val Cys Pro Val Leu Pro Gly Gly Leu 1 5 10 15
Phe Val Ala Leu Gly Trp Ile Phe Leu Leu Phe His Arg Asp Ala Phe
    20
                 25 30
Ser Leu His Thr Met Ser Ala Gly Phe Pro Lys Ser Pro Ala Asn Pro
   35 40
His His Pro Pro Leu Arg Leu Ser Pro
   50
                   55
```

```
<210> 166
    <211> 75
    <212> PRT
    <213> mouse
    <400> 166
Lys Thr Arg Arg Thr Leu Thr Gly Gln Leu Gly Leu Phe Ser Val Asp
1
          5 ` 10
Phe Met Val Cys Ile Phe Leu Phe Leu Phe Phe Cys Phe Leu Phe Pro
 20
                      25
                                   30
Phe Pro Leu Phe Leu Val Arg Lys His Ile Leu Leu Ser His Cys Lys
  35 40
                              45
Gln Trp Glu Gly Ser Thr Met Thr His Thr His Thr His Thr His Ile
 50 55
His Ile His Thr Pro Pro Arg Gln Cys Gln Ser
65
             70
    <210> 167
    <211> 52
    <212> PRT
    <213> mouse
    <400> 167
Val Arg Ser Leu Glu Gln Leu Gly Leu Phe Ser Val Asp Phe Met Val
          5
                           10
                                          15
Cys Ile Phe Leu Phe Leu Phe Phe Cys Phe Leu Phe Pro Phe Pro Leu
    20
                      25
                                  30
Phe Leu Val Arg Lys His Ile Leu Leu Ser His Cys Lys Gln Trp Glu
 35
              . 40
                                    45
Gly Ser Thr Met
  50
    <210> 168
    <211> 119
    <212> PRT
    <213> Rat
   <400> 168
Met Leu Gly Ala Thr Ser Leu Ser Trp Pro Trp Val Leu Trp Ala Val
          5
                   10
Ala Gln Arg Asp Ser Val Asp Ala Ile Gly Met Phe Leu Gly Gly Leu
   20 25
                                      .30
Val Ala Thr Ile Phe Leu Asp Ile Ile Tyr Ile Ser Ile Phe Tyr Ser
    35 40 45
Ser Val Ala Val Gly Asp Thr Gly Arg Phe Ser Ala Gly Met Ala Ile
                 55
                         . 60
Phe Ser Leu Leu Leu Gln Ala Leu Leu Leu Pro Arg Leu Pro His
            70 75
Ala Pro Gly Ser Glu Gly Val Ser Ser Arg Ser Ala Arg Ile Ser Ser
          85
                        90 95
Asp Leu Leu Arg Asn Ile Val Pro Thr Arg Gln Leu Thr Arg Gln Thr
    100
                         105
                                       110
His Leu Gln Thr Pro Leu Gln
     115
    <210> 169
    <211> 104
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<212> PRT
     <213> Rat
     <220>
     <400> 169
Leu Val Pro Lys Ser Ala Arg Ala Ser Leu Leu Cys Cys Gly Pro Lys
                                 10
Leu Ala Ala Cys Gly Ile Val Leu Ser Ala Trp Gly Val Ile Met Leu
         20
                             25
                                               30
Ile Met Leu Gly Ile Phe Phe Asn Val His Ser Ala Val Xaa Ile Xaa
      35
                        40
Asp Val Pro Phe Thr Glu Lys Asp Phe Glu Asn Gly Pro Gln Asn Ile
 50
                    55
                                        60
Tyr Asn Leu Tyr Glu Gln Val Ser Tyr Asn Cys Phe Ile Ala Ala Gly
                                    75
              70
Leu Tyr Leu Leu Xaa Gly Gly Phe Ser Phe Cys Gln Val Arg Leu Asn
             85
                                 90
Lys Arg Lys Glu Tyr Met Val Arg
      . 100
     <210> 170 ·
     <211> 123
     <212> PRT
     <213> Rat
     <220>
     <221> UNSURE
     <222> (27)...(27)
     <221> UNSURE
     <222> (104)...(104)
     <221> UNSURE
     <222> (118) ... (118)
     <400> 170
Met Arg Pro Gly Ala Asp Trp Ala Ala Val Cys Ala Leu Trp Pro Ser
              5
                              10
Trp Arg Pro Ser Cys Ser Leu Pro Ser Ser Xaa Arg Ile Gln Pro Asp
       20
                            25
Glu Leu Trp Leu Tyr Arg Asn Pro Tyr Val Lys Ala Glu Tyr Phe Pro
     35
                         40
                                            45
Thr Gly Pro Met Phe Val Ile Ala Phe Leu Thr Pro Leu Ser Leu Ile
                   55
                                      60
Phe Phe Ala Lys Phe Leu Arg Lys Ala Asp Ala Asp Arg Gln Arg Ala 65 70 75 80
Ser Leu Pro Arg Cys Gln Pro Cys Pro Ser Ala Lys Trp Cys Leu Tyr
             85
                               90
Gln His His Lys Thr Asp Ser Xaa Gln Gly His Ala Gln Ile Ala Ser
         100
                             105
Thr Glu Cys Ser Pro Xaa Gly Ile Ala His Ser
       115
                          120
     <210> 171
     <211> 75
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<212> PRT <213> Rat <400> 171 Ser Ala Gly Val Met Thr Ala Ala Val Phe Phe Gly Cys Ala Phe Ile 10 Ala Phe Gly Pro Ala Leu Ser Leu Tyr Val Phe Thr Ile Ala Thr Asp 20 · 25 30 Pro Leu Arg Val Ile Phe Leu Ile Ala Gly Ala Phe Phe Trp Leu Val 35 40 Ser Leu Leu Ser Ser Val Phe Trp Phe Leu Val Arg Val Ile Thr 50 55 Asp Asn Arg Asp Gly Pro Val Gln Asn Tyr Leu 65 70 <210> 172 <211> 79 <212> PRT <213> Human <400> 172 . Lys Thr Ser Tyr His Tyr His Thr Asn Val Glu Glu Leu Thr Ile Pro 1 5 . 10 Glu Thr Arg Asn Asn Leu Tyr Ile Ser Ile Ser Trp Leu Trp Cys Leu 20 25 30 Val Leu Val Leu Leu Ser Thr Met Ile Leu Asn Lys His Gly Trp Met 35 40 45 Lys Ala Asn Ala Tyr Ser Leu Val Pro Ser Ile Ile Tyr Ser Pro Ser 50 55 60 Tyr Leu Lys Leu Leu Leu Arg Leu Tyr Lys Leu Gln Ile Cys Cys · 70 <210> 173 <211> 134 <212> PRT <213> Human <220> <400> 173 Leu Arg Gly Arg Gly Arg Gly Val Cys Ser Gln Glu Ser Phe Gly Gly 5 10 15 Cys Cys Val Ser Gly Leu Ile Ala Met Gly Thr Lys Ala Gln Val Glu 20 25 30 Arg Lys Leu Cys Leu Phe Ile Leu Ala Ile Leu Leu Cys Ser Leu 35 40 45 Ala Leu Gly Ser Val Thr Val His Ser Ser Glu Pro Glu Val Arg Ile 55 60 ...

Pro Glu Asn Asn Pro Val Lys Leu Ser Cys Ala Tyr Ser Gly Phe Ser 65 70 75 80 70 75 Ser Pro Arg Val Glu Trp Lys Phe Asp Gln Gly Asp Thr Thr Arg Leu 85 90 95 Val Cys Tyr Asn Asn Lys Ile Thr Ala Ser Tyr Glu Asp Arg Val Thr 105 100 110 Phe Leu Pro Thr Gly Ile Thr Phe Lys Ser Val Thr Arg Glu Asp Thr 115 120 125 Gly Thr Tyr Thr Cys Met 130

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<210> 174
     <211> 137
     <212> PRT
     <213> Human
     <400> 174
Ala Trp Ser Arg Pro Arg Tyr Asp Ser Val Leu Ala Leu Ser Ala Ala
             5
                               10
Leu Gln Ala Thr Arg Ala Leu Met Val Val Ser Leu Val Leu Gly Phe
    20
                        25
                                          30
Leu Ala Met Phe Val Ala Thr Met Gly Met Lys Cys Thr Arg Cys Gly
     35
                      40
                                        45
Gly Asp Asp Lys Val Lys Lys Ala Arg Ile Ala Met Gly Gly Ile
                  55
                             60
Ile Phe Ile Val Ala Gly Leu Ala Ala Leu Val Ala Cys Ser Trp Tyr
                                75.
                 70
Gly His Gln Ile Val Thr Asp Phe Tyr Asn Pro Leu Ile Pro Thr Asn
            85
                             90
Ile Lys Tyr Glu Phe Gly Pro Ala Ile Phe Ile Gly Trp Ala Gly Ser 100 105 110
Ala Leu Val Ile Leu Gly Gly Ala Leu Ser Pro Val Pro Val Leu Gly
   115 120
Ile Arg Ala Gly Leu Gly Thr Cys Pro
  130
                    135
     <210> 175
     <211> 43
     <212> PRT
     <213> Human
    <400> 175
Met Lys Leu Ser Gly Met Phe Leu Leu Ser Leu Ala Leu Phe Cys
             5 10
Phe Leu Thr Gly Val Phe Ser Gln Gly Gly Gln Val Asp Cys Gly Glu
 20 25
                                             30
Ser Arg Thr Pro Arg Pro Thr Ala Leu Gly Asn
. 35
                       40
     <210> 176
     <211> 63
     <212> PRT
     <213> Rat
    <400> 176
Pro Asn Thr Arg Pro Arg Arg His Thr Ala Cys Arg Val Ser Ile Ser
             5 10 . 15
Val Phe Tyr Met Leu His Thr Glu Leu Lys Lys Cys Trp Phe Phe Leu 20 25 30
Phe Cys Phe Ser Leu Phe Leu Trp Phe Cys Phe Trp Phe Cys Phe Leu
    35
                      40
                                       45
Leu Pro Arg Phe Asp Tyr Leu Pro Met Pro Ser Thr Arg Pro Arg
   50
                    55
    <210> 177
   <211> 52
   <212> PRT
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<213> mouse <400> 177 eu Gln Gly P

Met Leu Gln Gly Pro Ala Pro Ser Cys Phe Trp Val Phe Ser Gly Ile

1 5 10 15

Cys Val Phe Trp Asp Phe Ile Phe Ile Ile Phe Phe Asn Val Leu Ser

Leu Gly Asn Arg Glu Ile Ser Ala Lys Asp Phe Ala Asp Gln Pro Ala 35 40 . 45

Gly Ala Gln Gly 50 .

<210> 178

<211> 62

<212> PRT

<213> mouse

<400> 178

Glu Pro Arg Ala Leu Phe Arg Pro Asp Lys Ala Leu Pro Leu Ser Cys 35 40 45

Ala Lys Pro Thr Ser Leu Cys Val Gln Ser Ser Phe Leu Gly 50 55 60

<210> 179

<211> 123

<212> PRT

<213> mouse

<400> 179

Ala Ser Arg Thr Ala Val Met Ser Leu Cys Arg Cys Gln Gln Gly Ser

1 5 10 15

Arg Ser Arg Met Asp Leu Asp Val Val Asn Met Phe Val Ile Ala Gly 20 25 30

Gly Thr Leu Ala Ile Pro Ile Leu Ala Phe Val Ala Ser Phe Leu Leu 35 40 45

Trp Pro Ser Ala Leu Ile Arg Ile Tyr Tyr Trp Tyr Trp Arg Arg Thr 50 60

Tyr Ser Phe Arg Gly Arg Pro Gly His Lys Pro Ser Ile Leu Met Leu
85 90 95

His Gly Phe Ser Ala His Lys Gly His Val Ala Gln Arg Gly Gln Val 100 105 . 110

Pro Ser Arg Lys Asn Leu His Phe Gly Cys Val

<210> 180

<211> 120

<212> PRT

<213> mouse

<220>

<221> UNSURE

PCT/NZ01/00099 WO 01/90357

> <222> (5)...(5) <400> 180

Ala Arg Arg Arg Xaa Arg Trp Arg Arg Gly Cys Cys Trp Leu Ile Gly
1 5 10 15 Thr Gly Leu Arg Ala Ala Thr Trp Thr Val Leu Cys Ser Pro Asn Ser 20 25 30 Ser Leu Val Val Ala Arg His Thr Lys Ser Phe Pro Pro Lys Lys Pro 35 40 45 Leu Gln Ala Leu Thr Met Ser Ile Met Asp His Ser Pro Thr Thr Gly 55 . 60 . Val Val Thr' Val Ile Val Ile Leu Ile Ala Ile Ala Ala Leu Gly Gly 65 70 75 80 Leu Ile Leu Gly Cys Trp Cys Tyr Leu Arg Leu Gln Arg Ile Ser Gln 85 90 95 Ser Glu Asp Glu Glu Ser Ile Val Gly Asp Gly Glu Thr Lys Glu Pro 100 105 Phe Tyr Trp Cys Ser Thr Leu Leu

115

<210> 181

<211> 60

<212> PRT

<213> mouse

<400> 181

Lys Gly Pro Glu Val Ser Cys Cys Ile Lys Tyr Phe Ile Phe Gly Phe 1 5 10 15 Asn Val Ile Phe Trp Phe Leu Gly Ile Thr Phe Leu Gly Ile Gly Leu 20 25 Trp Ala Trp Asn Glu Lys Gly Val Leu Ser Asn Ile Ser Ser Ile Thr 35 40 45 Asp Leu Gly Gly Phe Asp Pro Val Trp Leu Phe Leu

55 <210> 182

<211> 72

<212> PRT

<213> mouse

<220>

<400> 182

Lys Pro Thr Val Gly Ser Ala Glu Val Ala Ile Ala Val Phe Leu Val . 10 Ile Cys Ile Ile Val Val Leu Thr Ile Leu Gly Tyr Cys Phe Phe Lys 20 25 30 Asn Gln Arg Lys Glu Phe His Ser Pro Leu His His Pro Pro Pro Thr 35 40 45 Pro Ala Ser Ser Thr Val Ser Thr Thr Glu Asp Thr Glu His Leu Val 60 50 55 Tyr Asn His Thr Thr Gln Pro Leu

<210> 183 <211> 771

<212> PRT <213> Rat

<220>

<400> 183 Glu Leu Tyr Leu Asp Gly Asn Gln Phe Thr Leu Val Pro Lys Glu Leu 10 Ser Asn Tyr Lys His Leu Thr Leu Ile Asp Leu Ser Asn Asn Arg Ile 25 Ser Thr Leu Ser Asn Gln Ser Phe Ser Asn Met Thr Gln Leu Leu Thr 35 40 Leu Ile Leu Ser Tyr Asn Arg Leu Arg Cys Ile Pro Pro Arg Thr Phe 50 55 . 60 Asp Gly Leu Lys Ser Leu Arg Leu Leu Ser Leu His Gly Asn Asp Ile 65 70 75 . 80 Ser Val Val Pro Glu Gly Ala Phe Gly Asp Leu Ser Ala Leu Ser His 85 90 95 Leu Ala Ile Gly Ala Asn Pro Leu Tyr Cys Asp Cys Asn Met Gln Trp 100 105 110 Leu Ser Asp Trp Val Lys Ser Glu Tyr Lys Glu Pro Gly Ile Ala Arg 115 120 125 Cys Ala Gly Pro Gly Glu Met Ala Asp Lys Leu Leu Leu Thr Thr Pro 130 135 140 Lys Cys Asn Pro Cys Leu Ser Asn Pro Cys Lys Asn Asp Gly Thr Cys 165 170 175 Asn Asn Asp Pro Val Asp Phe Tyr Arg Cys Thr Cys Pro Tyr Gly Phe 180 185 190Lys Gly Gln Asp Cys Asp Val Pro Ile His Ala Cys Thr Ser Asn Pro 195 200 205 Cys Lys His Gly Gly Thr Cys His Leu Lys Pro Arg Arg Glu Thr Trp 210 215 220 Ile Trp Cys Thr Cys Ala Asp Gly Phe Glu Gly Glu Ser Cys Asp Ile 225 230 235 240 235 Asn Ile Asp Asp Cys Glu Asp Asn Asp Cys Glu Asn Asn Ser Thr Cys 245 250 255 Val Asp Gly IIe Asn Asn Tyr Thr Cys Leu Cys Pro Pro Glu Tyr Thr 260 265 270 Gly Glu Leu Cys Glu Glu Lys Leu Asp Phe Cys Ala Gln Asp Leu Asn 275 280 . Pro Cys Gln His Asp Ser Lys Cys Ile Leu Thr Pro Lys Gly Phe Lys 290 295 300 295 300 Cys Asp Cys Thr Pro Gly Tyr Ile Gly Glu His Cys Asp Ile Asp Phe 305 310 315 320 Asp Asp Cys Gln Asp Asn Lys Cys Lys Asn Gly Ala His Cys Thr Asp 325 330 335 Ala Val Asn Gly Tyr Thr Cys Val Cys Pro Glu Gly Tyr Ser Gly Leu 340 345 350 Phe Cys Glu Phe Ser Pro Pro Met Val Phe Leu Arg Thr Ser Pro Cys 355 360 . . 365 Asp Asn Phe Asp Cys Gln Asn Gly Ala Gln Cys Ile Ile Arg Val Asn 375 380 Glu Pro Ile Cys Gln Cys Leu Pro Gly Tyr Leu Gly Glu Lys Cys Glu 390

PCT/NZ01/00099 WO 01/90357

Lys Leu Val Ser Val Ser Ile Leu Val Asn Lys Glu Ser Tyr Leu Gln

Ile Pro Ser Ala Lys Val Arg Pro Gln Thr Asn Ile Thr Leu Gln Ile 425

410

430

405

420

```
Ala Thr Asp Glu Asp Ser Gly Ile Leu Leu Tyr Lys Gly Asp Lys Asp 435 440 445
His Ile Ala Val Glu Ser Ile Glu Gly Ile Arg Ala Ser Tyr Asp Thr
                  455
                                   460
Gly Ser His Pro Ala Ser Ala Ile Tyr Ser Val Glu Thr Ile Asn Asp
465
         470
                               475
Gly Asn Phe His Ile Val Glu Leu Leu Thr Leu Asp Ser Ser Leu Ser 485 490 495
Leu Ser Val Asp Gly Gly Ser Pro Lys Ile Ile Thr Asn Leu Ser Lys
       500 505
Gln Ser Thr Leu Asn Phe Asp Ser Pro Leu Tyr Val Gly Gly Met Pro
                520 ·
                                       525
     515
Gly Lys Asn Asn Val Ala Ser Leu Arg Gln Ala Pro Gly Gln Asn Gly
           535 . 540
  530
Thr Ser Phe His Gly Cys Ile Arg Asn Leu Tyr Ile Asn Ser Glu Leu 545 550 560
                                555
Gln Asp Phe Arg Lys Val Pro Met Gln Thr Gly Ile Leu Pro Gly Cys
            565
                             570 575
Glu Pro Cys His Lys Lys Val Cys Ala His Gly Thr Cys Gln Pro Ser
                           585
         580
                                            590
Ser Gln Ser Gly Phe Thr Cys Glu Cys Glu Glu Gly Trp Met Gly Pro
                      600
                                        605
Leu Cys Asp Gln Arg Thr Asn Asp Pro Cys Leu Gly Asn Lys Cys Val
                         620
 610
         615
His Gly Thr Cys Leu Pro Ile Asn Ala Phe Ser Tyr Ser Cys Lys Cys
             630
                     635
Leu Glu Gly His Gly Gly Val Leu Cys Asp Glu Glu Glu Asp Leu Phe
645 650 655
            645
                             -650
                                                655
Asn Pro Leu Pro Gly Asp Gln Val Gln Ala Arg Glu Val Gln Ala Leu
        660
                        665
                                          670
Trp Ala Arg Ala Ala Leu Leu Trp Met Gln Gln Trp Ile His Arg Gly
    675 680 685
Gln Leu Thr Gln Arg Ile Ser Cys Arg Gly Glu Arg Ile Arg Asp Tyr
. 690
                    695
                                   700
Tyr Gln Ser Ser Arg Val Arg Cys Leu Ser Asn Asp
     <210> 184
    <211> 340
     <212> PRT
     <213> mouse
     <400> 184
Asp Gly Ser Leu Trp Leu Gln Ala Thr Gln Pro Asp Asp Ala Gly His
                              10
Tyr Thr Cys Val Pro Ser Asn Gly Phe Leu His Pro Pro Ser Ala Ser
   20
                           25
                                           30
Ala Tyr Leu Thr Val Leu Tyr Pro Ala Gln Val Thr Val Met Pro Pro
     · 35
                       40
                                         45
```

Glu Thr Pro Leu Pro Thr Gly Met Arg Gly Val Ile Arg Cys Pro Val

Arg Ala Asn Pro Pro Leu Leu Phe Val Thr Trp Thr Lys Asp Gly Gln 65 70 75 80 Ala Leu Gln Leu Asp Lys Phe Pro Gly Trp Ser Leu Gly Pro Glu Gly

50 . 55

```
Ser Leu Ile Ile Ala Leu Gly Asn Glu Asp Ala Leu Gly Glu Tyr Ser
          100
                         105
                                             110
Cys Thr Pro Tyr Asn Ser Leu Gly Thr Ala Gly Pro Ser Pro Val Thr
             120
Arg Val Leu Leu Lys Ala Pro Pro Ala Phe Ile Asp Gln Pro Lys Glu
130 135 140
Glu Tyr Phe Gln Glu Val Gly Arg Glu Leu Leu Ile Pro Cys Ser Ala
      150
                           155
Arg Gly Asp Pro Pro Pro Ile Val Ser Trp Ala Lys Val Gly Arg Gly
                      170
         165
                                                 175
Leu Gln Gly Gln Ala Gln Val Asp Ser Asn Asn Ser Leu Val Leu Arg
180 185 190
          180
                           185
                                           190
Pro Leu Thr Lys Glu Ala Gln Gly Arg Trp Glu Cys Ser Ala Ser Asn
     195
                      200
                                205
Ala Val Ala Arg Val Thr Thr Ser Thr Asn Val Tyr Val Leu Gly Thr
                    215
                                      220
Ser Pro His Val Val Thr Asn Val Ser Val Val Pro Leu Pro Lys Gly
        230
Ala Asn Val Ser Trp Glu Pro Gly Phe Asp Gly Gly Tyr Leu Gln Arg
245 250 255
Phe Ser Val Trp Tyr Thr Pro Leu Ala Lys Arg Pro Asp Arg Ala His
    260
                        265
His Asp Trp Val Ser Leu Ala Val Pro Ile Gly Ala Thr His Leu Leu
              280 .
     275
                                      285
Val Pro Gly Leu Gln Ala His Ala Gln Tyr Gln Phe Ser Val Leu Ala 290 295 300
Gln Asn Lys Leu Gly Ser Gly Pro Phe Ser Glu Ile Val Leu Ser Ile
305 310 315 320
Pro Glu Gly Leu Pro Thr Thr Pro Ala Ala Pro Gly Leu Pro Ala Thr
          325
                              330
Arg Ser Arg Val
         340
     <210> 185
     <211> 536
     <212> PRT
     <213> mouse
     <400> 185
Lys Val Glu Gly Glu Gly Arg Gly Arg Trp Ala Leu Gly Leu Leu Arg
1
                        10
Thr Phe Asp Ala Gly Glu Phe Ala Gly Trp Glu Lys Val Gly Ser Gly
         20
                           25
Gly Phe Gly Gln Val Tyr Lys Val Arg His Val His Trp Lys Thr Trp 35 40 45
Leu Ala Ile Lys Cys Ser Pro Ser Leu His Val Asp Asp Arg Glu Arg
                55
                                     60
Met Glu Leu Leu Glu Glu Ala Lys Lys Met Glu Met Ala Lys Phe Arg
              70
                                 75
Tyr Ile Leu Pro Val Tyr Gly Ile Cys Gln Glu Pro Val Gly Leu Val
             85
                              90
Met Glu Tyr Met Glu Thr Gly Ser Leu Glu Lys Leu Leu Ala Ser Glu
                  105
Pro Leu Pro Trp Asp Leu Arg Phe Arg Ile Val His Glu Thr Ala Val
```

Gly Met Asn Phe Leu His Cys Met Ser Pro Pro Leu Leu His Leu Asp

```
130
                   135
Leu Lys Pro Ala Asn Ile Leu Leu Asp Ala His Tyr Gln Met Ser Arg
                        155
       150
Phe Leu Asp Phe Gly Leu Ala Lys Cys Asn Gly Met Ser His Ser His 165 170 175
Asp Leu Ser Met Asp Gly Leu Phe Gly Thr Ile Gly Tyr Leu Pro Pro
   180 185 190
Glu Arg Ile Arg Glu Lys Ser Arg Leu Phe Asp Thr Lys His Asp Val
                       200
      195
                                       205
Tyr Ser Phe Ala Ile Val Ile Trp Gly Val Leu Thr Gln Asn Asn Pro
           215
                                   220
Phe Ala Asp Glu Lys Asn Ile Leu His Ile Met Met Lys Val Val Lys 225 230 235 240
Gly His Arg Pro Glu Leu Pro Pro Ile Cys Arg Pro Arg Pro Arg Ala 245 250 255
Cys Ala Ser Leu Ile Gly Leu Met Gln Arg Cys Trp His Ala Asp Pro
         260
                          265
                                           270
Gln Val Arg Pro Thr Phe Gln Glu Ile Thr Ser Glu Thr Glu Asp Leu
275 280 285
Cys Glu Lys Pro Asp Glu Glu Val Lys Asp Leu Ala His Glu Pro Gly
 290 . 295
                                    300
Glu Lys Ser Ser Leu Glu Ser Lys Ser Glu Ala Arg Pro Glu Ser Ser
305 310
                                 315
Arg Leu Lys Arg Ala Ser Ala Pro Pro Phe Asp Asn Asp Cys Ser Leu
        325 · 330 335
Ser Glu Leu Ser Gln Leu Asp Ser Gly Ile Phe Pro Arg Leu Leu 340 345 350
Lys Gly Pro Glu Glu Leu Ser Arg Ser Ser Ser Glu Cys Lys Leu Pro 355 360 365
Ser Ser Ser Ser Gly Lys Arg Leu Ser Gly Val Ser Ser Val Asp Ser
 370
           375
                                     380
Ala Phe Ser Ser Arg Gly Ser Leu Ser Leu Ser Phe Glu Arg Glu Ala 385 390 395 400
Ser Thr Gly Asp Leu Gly Pro Thr Asp Ile Gln Lys Lys Lys Leu Val
            405 410 415
Asp Ala Ile Ile Ser Gly Asp Thr Ser Arg Leu Met Lys Ile Leu Gln
                       425
                               . 430
        420
Pro Gln Asp Val Asp Leu Val Leu Asp Ser Ser Ala Ser Leu Leu His
     435 440 445
Leu Ala Val Glu Ala Gly Gln Glu Glu Cys Val Lys Trp Leu Leu Leu
           455 460
Asn Asn Ala Asn Pro Asn Leu Thr Asn Arg Lys Gly Ser Thr Pro Leu
               470
                                 475
His Met Ala Val Glu Arg Lys Gly Arg Gly Ile Val Glu Leu Leu
           485
                   490
Ala Arg Lys Thr Ser Val Asn Ala Lys Asp Glu Asp Gln Trp Thr Aļa
        500 505
                                           _, 510
Leu His Phe Ala Ala Gln Asn Gly Asp Glu Gly Gln His Lys Ala Ala
    515 520
                                         525
Ala Arg Glu Glu Cys Phe Cys Gln
     <210> 186
     <211> 337
     <212> PRT
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<213> Rat

<220>

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<400> 186
Arg Phe Gly Tyr Gln Met Asp Glu Gly Asn Gln Cys Val Asp
 Val Asp Glu Cys Ala Thr Asp Ser His Gln Cys Asn Pro Thr Gln Ile
20 25 30
 Cys Ile Asn Thr Glu Gly Gly Tyr Thr Cys Ser Cys Thr Asp Gly Tyr
35 40 45
 Trp Leu Leu Glu Gly Gln Cys Leu Asp Ile Asp Glu Cys Arg Tyr Gly 50 55 60
 Tyr Cys Gln Gln Leu Cys Ala Asn Val Pro Gly Ser Tyr Ser Cys Thr 65 70 75 . 80
 Cys Asn Pro Gly Phe Thr Leu Asn Asp Asp Gly Arg Ser Cys Gln Asp
              85
                                  90
 Val Asn Glu Cys Glu Thr Glu Asn Pro Cys Val Gln Thr Cys Val Asn
          100
                     105 110
 Thr Tyr Gly Ser Phe Ile Cys Arg Cys Asp Pro Gly Tyr Glu Leu Glu
115 120 125
Glu Asp Gly Ile His Cys Ser Asp Met Asp Glu Cys Ser Phe Ser Glu
130 135 140
                     135 140
Phe Leu Cys Gln His Glu Cys Val Asn Gln Pro Gly Ser Tyr Phe Cys 145 150 155 160
 Ser Cys Pro Pro Gly Tyr Val Leu Leu Glu Asp Asn Arg Ser Cys Gln
165 170 175
 Asp Ile Asn Glu Cys Glu His Arg Asn His Thr Cys Thr Pro Leu Gln
180 185 190
 Thr Cys Tyr Asn Leu Gln Gly Gly Phe Lys Cys Ile Asp Pro Ile Val
195 200 205
 Ala Glu Asn Thr Gly Cys Arg Asp Gln Pro Phe Thr Ile Leu Phe Arg 225 230 235 240
 Asp Met Asp Val Val Ser Gly Arg Ser Val Pro Ala Asp Ile Phe Gln
             245 250 255
Met Gln Ala Thr Thr Arg Tyr Pro Gly Ala Tyr Tyr Ile Phe Gln Ile
. 260 265 270
 Lys Ser Gly Asn Glu Gly Arg Glu Phe Tyr Met Arg Gln Thr Gly Pro
275 280 285
 Ile Ser Ala Thr Leu Val Met Thr Arg Pro Ile Lys Gly Pro Arg Asp 290 295 300
 Ile Gln Leu Asp Leu Glu Met Ile Thr Val Asn Thr Val Ile Asn Phe
 305 310 315 320
 Arg Gly Ser Ser Val Ile Arg Leu Arg Ile Tyr Val Ser Gln Tyr Pro
             325 . 330
                                                     335
 Phe
```

<210> 187

<211> 152

<212> PRT

<213> mouse

<400> 187

Met Ala Leu Gly Val Leu Ile Ala Val Cys Leu Leu Phe Lys Ala Met 1 5 . 10 15

PCT/NZ01/00099 WO 01/90357

```
Lys Ala Ala Leu Ser Glu Glu Ala Glu Val Ile Pro Pro Ser Thr Ala .
           20
                             25
Gln Gln Ser Asn Trp Thr Phe Asn Asn Thr Glu Ala Asp Tyr Ile Glu
      35
                        40
Glu Pro Val Ala Leu Lys Phe Ser His Pro Cys Leu Glu Asp His Asn
                    55
                                       60
Ser Tyr Cys Ile Asn Gly Ala Cys Ala Phe His His Glu Leu Lys Gln
        70 .
                                  75
Ala Ile Cys Arg Cys Phe Thr Gly Tyr Thr Gly Gln Arg Cys Glu His 85 90 95
Leu Thr Leu Thr Ser Tyr Ala Val Asp Ser Tyr Glu Lys Tyr Ile Ala 100 105 110
Ile Gly Ile Gly Val Gly Leu Leu Ile Ser Ala Phe Leu Ala Val Phe
   115 120
                                 125
Tyr Cys Tyr Ile Arg Lys Arg Cys Ile Asn Leu Lys Ser Pro Tyr Ile
                    135
  130
                                  140
Ile Cys Ser Gly Gly Ser Pro Leu
     <210> 188
     <211> 118
     <212> PRT
     <213> Rat
     <220>
     <400> 188
Leu Val Pro Gln Phe Gly Thr Arg Ile Arg Tyr ThrAla Tyr Asp Arg
              5
Ala Tyr Asn Arg Ala Ser Cys Lys Phe Ile Val·Lys Val Gln Val Arg
        20
                         · 25
Arg Cys Pro Ile Leu Lys Pro Pro Gln His Gly Tyr Leu Thr Cys Ser 35 40 .45
Ser Ala Gly Asp Asn Tyr Gly Ala Ile Cys Glu Tyr His Cys Asp Gly
  50 55
                                    60
Gly Tyr Glu Arg Gln Gly Thr Pro Ser Arg Val Cys Gln Ser Ser Arg
               70
                                   75
Gln Trp Ser Gly Ser Pro Pro Val Cys Thr Pro Met Lys Ile Asn Val
                               90
           85
                                                 95
Asn Val Asn Ser Ala Ala Gly Leu Leu Asp Gln Phe Tyr Glu Lys Gln
         100
                   105
Arg Leu Leu Ile Val Ser
      115
     <210> 189
     <211> 299
     <212> PRT
     <213> Human
     <220>
     <400> 189
Met Gly Thr Lys Ala Gln Val Glu Arg Lys Leu Cys Leu Phe Ile
                              10
Leu Ala Ile Leu Cys Ser Leu Ala Leu Gly Ser Val Thr Val His
                    25
```

20

Ser Ser Glu Pro Glu Val Arg Ile Pro Glu Asn Asn Pro Val Lys Leu

30

```
35
                        40
Ser Cys Ala Tyr Ser Gly Phe Ser Ser Pro Arg Val Glu Trp Lys Phe
           55
Asp Gln Gly Asp Thr Thr Arg Leu Val Cys Tyr Asn Asn Lys Ile Thr 65 70 75 80
Ala Ser Tyr Glu Asp Arg Val Thr Phe Leu Pro Thr Gly Ile Thr Phe 85 90 95
Lys Ser Val Thr Arg Glu Asp Thr Gly Thr Tyr Thr Cys Met Val Ser
         100
                  105
                                  110
Glu Glu Gly Gly Asn Ser Tyr Gly Glu Val Lys Val Lys Leu Ile Val
115 120 125
Leu Val Pro Pro Ser Lys Pro Thr Val Asn Ile Pro Ser Ser Ala Thr 130 135 140
Ile Gly Asn Arg Ala Val Leu Thr Cys Ser Glu Gln Asp Gly Ser Pro
145 150 155
Pro Ser Glu Tyr Thr Trp Phe Lys Asp Gly Ile Val Met Pro Thr Asn
165 170 175
                                        175
Pro Lys Ser Thr Arg Ala Phe Ser Asn Ser Ser Tyr Val Leu Asn Pro
180
                  185 190
Thr Thr Gly Glu Leu Val Phe Asp Pro Leu Ser Ala Ser Asp Thr Gly 195 200 205
Glu Tyr Ser Cys Glu Ala Arg Asn Gly Tyr Gly Thr Pro Met Thr Ser
 210 215
                             220
Asn Ala Val Arg Met Glu Ala Val Glu Arg Asn Val Gly Val Ile Val
       230 235
Ala Ala Val Leu Val Thr Leu Ile Leu Leu Gly Ile Leu Val Phe Gly 245 250 255
Ile Trp Phe Ala Tyr Ser Arg Gly His Phe Asp Arg Thr Lys Lys Gly 260 265 270
Thr Ser Ser Lys Lys Val Ile Tyr Ser Gln Pro Ser Ala Arg Ser Glu
      275
                       280
Gly Glu Phe Lys Gln Thr Ser Ser Phe Leu Val
  290 .
                    295
    <210> 190
    <211> 91
     <212> PRT
     <213> Human
    <400> 190
Gln Pro Thr Val Phe Trp Pro Lys Thr Ser Ala Lys Lys Gly Asn Trp
1 5
                    10 . 15 .
Val Leu Arg Leu Gly Leu Ser Asn Pro Asp Arg Pro Ala Arg Gln Asn
         20
                 25
Asn Trp Phe Leu Pro Ala Ser Arg Glu Ile Pro Glu His Ser Ala Leu
                  40
  35
                                      45
Thr Arg Tyr Pro Ala Gln Ile Arg Gly Cys Trp Pro His Arg Leu Thr 50 60
Lys Pro Gln Thr Cys Leu Pro Gln Ala Arg Ser Tyr Leu Ser His Glu
                70 75
Val Thr Gln Ala Thr Arg Thr Cys Pro Gly Gly
             85
     <210> 191
     <211> 89
     <212> PRT
```

<213> mouse

<210> 192 <211> 299 <212> PRT <213> mouse

<220>

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Asn Glu Ile Gly Val Gly Pro Phe Ser Gln Phe Ile Lys Ala Lys Thr
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Arg Pro Leu Pro Pro Ser Pro Pro Arg Leu Glu Cys Ala Ala Ser Gly
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Pro Gln Ser Leu Lys Leu Lys Trp Gly Asp Ser Asn Ser Lys Thr His
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Arg Phe Ile Ser Ile Tyr Arg Gly Pro Ser His Thr Tyr Lys Val Gln
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Arg Leu Thr Glu Phe Thr Cys Tyr Ser Phe Arg Ile Gln Ala Met Ser
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Glu Ala Gly Glu Gly Pro Tyr Ser Glu Thr Tyr Thr Phe Ser Thr Thr 145 150 155 160
Lys Ser Val Pro Pro Thr Leu Lys Ala Pro Arg Val Thr Gln Leu Glu
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Gly Asn Ser Cys Glu Ile Phe Trp Glu Thr Val Pro Pro Met Arg Gly
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Asp Pro Val Ser Tyr Val Leu Gln Val Leu Val Gly Arg Asp Ser Glu
195 200 205
Tyr Lys Gln Val Tyr Lys Gly Glu Ala Thr Phe Gln Ile Ser Gly 210 215 220
Leu Glm Ser Asn Thr Asp Tyr Arg Phe Arg Val Cys Ala Cys Arg Arg
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Cys Val Asp Thr SerGln Glu Leu Ser Gly Ala Phe Ser Pro Ser Ala 245 250 255
Ala Phe Met Leu Gln Gln Arg Glu Val Met Leu Thr Gly Asp Leu Gly 260 265 270
Gly Met Glu Glu Ala Lys Met Lys Gly Met Met Pro Thr Asp Glu Gln
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Phe Ala Ala Leu Ile Val Leu Gly Phe Ala Thr Leu Ser Ile Leu Phe
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420

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<400> 218

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1080

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| aacagtggac ctcaatgatg | gaagggctgc | catctgtggc | cacacaagaa | gccaccatgc | 180 |
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His Pro Thr Leu Asn Leu Pro Leu Ser Ala Gln Gly Thr Val Lys Thr
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Trp Lys Asn

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Leu Ile Arg Tyr Gly Lys Thr Lys Gln Ser Gly Ser Arg Arg Pro Ala
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65 70 75 80
Val Val Ser Val Leu Trp Asn Gly Ser Leu Leu Trp Phe Leu Ser Gln
Ser Leu Phe Leu Gly Ala Pro Phe Pro Ser Trp Leu Trp Ala Leu Leu 100 105 \cdot 110
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Ala Ser Arg Ile Gln Ala Gly Glu Leu Ala Leu Ser Thr Phe Leu Val
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Tyr Val Ser Val Phe Ser Asn Thr Ala Ile His Val Val Gln Tyr Cys
165 170 175
Phe Gly Leu Val Tyr Tyr Val Leu Val Gly Leu Thr Val Leu Ser Gln
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Val Pro Met Asn Asp Lys Asn Val Tyr Ala Leu Gly Lys Asn Leu Leu
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Leu Gln Ala Arg Trp Phe His Ile Leu Gly Met Met Met Phe Phe Trp
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Ser Ser Ala His Gln Tyr Lys Cys His Val Ile Leu Ser Asn Leu Arg
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Arg Asn Lys Lys Gly Val Val Ile His Cys Gln His Arg Ile Pro Phe
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Gly Asp Trp Phe Glu Tyr Val Ser Ser Ala Asn Tyr Leu Ala Glu Leu
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Met Ile Tyr Ile Ser Met Ala Val Thr Phe Gly Leu His Asn Val Thr 275 280 285
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Trp Trp Leu Val Val Thr Tyr Val Phe Phe Ser Gln Ala Leu Ser Ala
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His Arg Lys Ala Phe Leu Pro Phe Leu Phe
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Phe Arg Gly Tyr Gln Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Ile
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                                         60
Pro Gly Asn His Gly Asn Asn Gly Asn Asn Gly Ala Thr Gly His Glu
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Gly Ala Lys Gly Glu Lys Gly Asp Lys Gly Asp Leu Gly Pro Arg Gly
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Glu Arg Gly Gln His Gly Pro Lys Gly
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                                                  30
Pro Ile Trp Trp Gly Thr Gln Arg Arg Gly Ser Glu Thr Met Ala Gly
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                          40
                                             45
Ala Ala Val Lys Tyr Leu Ser Gln Glu Glu Ala Gln Ala Val Asp Gln
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                                        60 -
Glu Leu Phe Asn Glu Tyr Gln Phe Ser Val Asp Gln Leu Met Glu Leu
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Ala Gly Leu Ser Cys Ala Thr Ala Ile Ala Lys Ala Tyr Pro Pro Thr
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Ser Met Ser Lys Ser Pro Pro Thr Val Leu Val Ile Cys Gly Pro Gly

Asn Asn Gly Gly Asp Gly Leu Val Cys Ala Arg His Leu Lys Leu Phe 120

Gly Tyr Gln Pro Thr Ile Tyr Tyr Pro Lys Arg Pro Asn Lys Pro Leu

100 . 105

135

115

125



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Leu Ala His Ala Ala Phe Ser Ala Ala Gln His Arg Ser Tyr Met Arg
                            25
                                             30
         20
Leu Thr Glu Lys Glu Asp Glu Ser Leu Pro Ile Asp Ile Val Leu Gln
                         40
Thr Leu Leu Ala Phe Ala Val Thr Cys Tyr Gly Ile Val His Ile Ala
  50
                     55
                                       60
Gly Glu Phe Lys Asp Met Asp Ala Thr Ser Glu Leu Lys Asn Lys Thr
                                  75
               70
Phe Asp Thr Leu Arg Asn His Pro Ser Phe Tyr Val Phe Asn His Arg
                     90
           85
                                        95
Gly Arg Val Leu Phe Arg Pro Ser Asp Ala Thr Asn Ser Ser Asn Leu
         100
                           105
                                             110
Asp Ala Leu Ser Ser Asn Thr Ser Leu Lys Leu Arg Lys Phe Asp Ser
                         120
      115
                                           125
Leu Arg Arg
   130
     <210> 285
     <211> 78
     <212> PRT
     <213> Mouse
     <400> 285
Gly Thr Arg Lys Pro Leu Pro Met Glu Ala His Ser Arg Arg Glu Lys
1 5 10 · 15
Ala Ser Gly Leu Arg Leu Ala Trp His Tyr Glu Cys Ser Gly Val Ser
                            25
          20
Val Trp Trp Met Cys Val Leu Gly Trp Leu Ser Phe Leu Val Phe Leu
                         40
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Leu Phe Ser Leu Val Cys Ser Phe Pro Ser Pro Ile Asn His Ser His 50 55 60

Met Leu Pro Cys Leu Phe Leu Arg Gly Gly Gly Ser Asn Val 75

<210> 286 <211> 206 <212> PRT <213> Mouse

<400> 286

Met Leu Pro Pro Ala Ile His Leu Ser Leu Ile Pro Leu Leu Cys Ile 10 Leu Met Arg Asn Cys Leu Ala Phe Lys Asn Asp Ala Thr Glu Ile Leu 20 25 30 Tyr Ser His Val Val Lys Pro Val Pro Ala His Pro Ser Ser Asn Ser 35 40 45 Thr Leu Asn Gln Ala Arg Asn Gly Gly Arg His Phe Ser Ser Thr Gly 50 55 60 Leu Asp Arg Asn Ser Arg Val Gln Val Gly Cys Arg Glu Leú Arg Ser 70 Thr Lys Tyr Ile Ser Asp Gly Gln Cys Thr Ser Ile Ser Pro Leu Lys 85 90 Glu Leu Val Cys Ala Gly Glu Cys Leu Pro Leu Pro Val Leu Pro Asn 100 . 105 110 Trp Ile Gly Gly Tyr Gly Thr Lys Tyr Trp Ser Arg Arg Ser Ser 120 115 125 Gln Glu Trp Arg Cys Val Asn Asp Lys Thr Arg Thr Gln Arg Ile Gln 130 135 140 Leu Gln Cys Gln Asp Gly Ser Thr Arg Thr Tyr Lys Ile Thr Val Val 145 150 150 160 Thr Ala Cys Lys Cys Lys Arg Tyr Thr Arg Gln His Asn Glu Ser Ser 165 170 175 His Asn Phe Glu Ser Val Ser Pro Ala Lys Pro Ala Gln His His Arg 180 185 190 Glu Arg Lys Arg Ala Ser Lys Ser Ser Lys His Ser Leu Ser 195 200

<210> 287 <211> 169 <212> PRT <213> Mouse

<400> 287

Met Ser Gly Leu Arg Thr Leu Leu Gly Leu Gly Leu Leu Val Ala Gly 1 10 15 Ser Arg Leu Pro Arg Val Ile Ser Gln Gln Ser Val Cys Arg Ala Arg 25 20 . 30 Pro Ile Trp Trp Gly Thr Gln Arg Arg Gly Ser Glu Thr Met Ala Gly 35 40 45 .Ala Ala Val Lys Tyr Leu Ser Gln Glu Glu Ala Gln Ala Val Asp Gln 50 60 55 Glu Leu Phe Asn Glu Tyr Gln Phe Ser Val Asp Gln Leu Met Glu Leu 70 75 Ala Gly Leu Ser Cys Ala Thr Ala Ile Ala Lys Ala Tyr Pro Pro Thr 85 Ser Met Ser Lys Ser Pro Pro Thr Val Leu Val Ile Cys Gly Pro Gly

```
110
Asn Asn Gly Gly Asp Gly Leu Val Cys Ala Arg His Leu Lys Leu Phe
                        120
      115
                                             125
Gly Tyr Gln Pro Thr Ile Tyr Tyr Pro Lys Arg Pro Asn Lys Pro Leu
                       135
                                          140
Phe Thr Gly Leu Val Thr Gln Cys Gln Lys Met Asp Ile Pro Phe Leu
                 150
                                      155
Gly Glu Met Pro Pro Glu Asp Gly Met
               165
      <210> 288
      <211> 114
      <212> PRT
      <213> Mouse
      <400> 288
Met Ser Val Thr Ile Gly Arg Leu Ala Leu Phe Leu Ile Gly Ile Leu
                                  10
Leu Cys Pro Val Ala Pro Ser Leu Thr Arg Ser Trp Pro Gly Pro Asp
           20
                               25
Thr Cys Ser Leu Phe Leu Gln His Ser Leu Ser Leu Ser Leu Arg Leu
                          40
                                              45
Gly Gln Ser Leu Glu Gly Gly Leu Ser Val Cys Phe His Val Cys Ile
   50
                       55
                                         60
His Ala Cys Glu Cys Val Ala Cys Cys Arg Val Leu Trp Asp Pro Lys
                   70
                                      75
Pro Arg Gly Ser Ser Leu Cys Arg Trp Val Leu Gly Ser Ile Thr Cys
                                90
               85
Leu Phe Met Tyr Glu Val Gly Gly Trp Thr Gln Gly Gly Leu Ile Val
                               105
            100
Ser Leu
      <210> 289
      <211> 46
      <212> PRT
      <213> Mouse
      <400> 289
Met His Tyr Pro Cys Leu Ala Cys Leu Phe Val Asn Val His Trp Cys
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Phe Ala Trp Met Cys Ile Leu Val Lys Met Ser Glu Leu Leu Glu Leu
          20
                              25
                                                  30
Glu Leu Glu Thr Met Val Ser Cys Leu Val Asp Val Gly Asn
       35
                           40
   · <210> 290
      <211> 199
      <212> PRT
      <213> Mouse
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Met Val Leu Pro Thr Val Leu Ile Leu Leu Ser Trp Ala Ala Gly
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Leu Gly Gly Glu Thr Arg Pro Arg Ala Ala Thr Glu Arg Arg Ser Val
           20
                               25
                                                  30
Gly Pro Ser Ala Arg Arg Gly Ala Gly Pro Arg Val Ser Gly Leu Leu
```



```
Gly Phe Cys Gln Leu Ser Gln Leu Ala Ser Ala Asp Pro Glu Arg Arg
                       55
                                          60
Ser Pro Arg Ala Ile Val Pro Arg Ala Pro Arg Pro Arg Ser Arg Arg
                   70
Arg Pro Cys Leu Pro Gly Phe Ser Arg Arg Phe Pro Arg Glu Arg Arg
               85
                                  90
Ser Pro Gly Gln Pro Pro Ser Arg Thr Pro Gln Pro Pro Gln Pro Cys
                              105
           100
Arg Gly Pro Ser Pro Gly Thr Ala Gln Thr Arg Ser Asn Leu Arg Gly
                           120
                                              125
       115
Trp Gln Arg Gly Gly Ser Ile Val Leu Gln Ala Ser Glu Arg Thr Arg
                      135
                                          140
Ala Gly Cys Arg Thr Pro Val Cys Val Ser His Pro Ser Ala Phe Pro
              150
                                    155
Pro Pro Arg Ala Leu Phe Gly Val Phe Val Ala Ser Ala Pro Glu Val
                                170
              165
                                                   . 175
Val Cys Val Cys Val Ser Val Val Leu Ser Val Cys Leu Leu Ser Pro
                                                  190
           180
                               185
Arg Gly Lys Thr Leu Val Asp
       195
      <210> 291
      <211> 568
      <212> PRT
      <213> Rat
      <400> 291
Met Glu Leu Leu Tyr Trp Cys Leu Leu Cys Leu Leu Leu Pro Leu Thr
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Ser Arg Thr Gln Lys Leu Pro Thr Arg Asp Glu Glu Leu Phe Gln Met
                               25
                                                   30
           20
Gln Ile Arg Asp Lys Ala Leu Phe His Asp Ser Ser Val Ile Pro Asp
                         40
      35
Gly Ala Glu Ile Ser Ser Tyr Leu Phe Arg Asp Thr Pro Arg Arg Tyr
                       55
                                          60
Phe Phe Met Val Glu Glu Asp Asn Thr Pro Leu Ser Val Thr Val Thr
                  70
Pro Cys Asp Ala Pro Leu Glu Trp Lys Leu Ser Leu Gln Glu Leu Pro
                                  90
               85 ·
Glu Glu Ser Ser Ala Asp Gly Ser Gly Asp Pro Glu Pro Leu Asp Gln
                               105
                                                  110
           100
Gln Lys Gln Gln Met Thr Asp Val Glu Gly Thr Glu Leu Phe Ser Tyr
115 120 125
        115
                           120
Lys Gly Asn Asp Val Glu Tyr Phe Leu Ser Ser Ser Pro Ser Gly
                       135
                                          140
    130
Leu Tyr Gln Leu Glu Leu Leu Ser Thr Glu Lys Asp Thr His Phe Lys
                                     155
                   150
Val Tyr Ala Thr Thr Thr Pro Glu Ser Asp Gln Pro Tyr Pro Asp Leu
165 170 . 175
                                   170
Pro Tyr Asp Pro Arg Val Asp Val Thr Ser Ile Gly Arg Thr Thr Val
                              185
           180
Thr Leu Ala Trp Lys Gln Ser Pro Thr Ala Ser Met Leu Lys Gln Pro
                           200
                                            205
        195
Ile Glu Tyr Cys Val Val Ile Asn Lys Glu His Asn Phe Lys Ser Leu
                                           220
                       215
Cys Ala Ala Glu Thr Lys Met Ser Ala Asp Asp Ala Phe Met Val Ala
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```
230
Pro Lys Pro Gly Leu Asp Phe Ser Pro Phe Asp Phe Ala His Phe Gly
                                  250
               245
Phe Pro Thr Asp Asn Leu Gly Lys Asp Arg Ser Phe Leu Ala Lys Pro
                               265
                                                  270
          260
Ser Pro Lys Val Gly Arg His Val Tyr Trp Arg Pro Lys Val Asp Ile
        275
                           280
                                              285
Lys Lys Ile Cys Ile Gly Ser Lys Asn Ile Phe Thr Val Ser Asp Leu
                    295
                                          300
Lys Pro Asn Thr Gln Tyr Tyr Phe Asp Val Phe Met Val Asn Thr Asn
                   310
                                      315
Thr Asn Met Asn Thr Ala Phe Val Gly Ala Phe Ala Arg Thr Lys Glu
              325
                                  330
                                                      335
Glu Ala Lys Gln Lys Thr Val Glu Leu Lys Asp Gly Arg Val Thr Asp 340 345 350
           340
                              345
Val Val Lys Arg Lys Gly Lys Lys Phe Leu Arg Phe Ala Pro Val 355 360 365
       355.
                                              365
Ser Ser His Gln Lys Val Thr Leu Phe Ile His Ser Cys Met Asp Thr
                       375
                                          380
Val Gln Val Gln Val Arg Arg Asp Gly Lys Leu Leu Leu Ser Gln Asn
                                       395
                   390
Val Glu Gly Ile Arg Gln Phe Gln Leu Arg Gly Lys Pro Lys Gly Lys
                                 410
               405
                                                      415
Tyr Leu Ile Arg Leu Lys Gly Asn Lys Lys Gly Ala Ser Met Leu Lys
                              425
           420
                                                  430
Ile Leu Ala Thr Thr Arg Pro Ser Lys His Ala Phe Pro Ser Leu Pro
                          440
                                             445
       435
Asp Asp Thr Arg Ile Lys Ala Phe Asp Lys Leu Arg Thr Cys Ser Ser
                      455
                                          460
    450
Val Thr Val Ala Trp Leu Gly Thr Gln Glu Arg Arg Lys Phe Cys Ile
                   470
                                     475
Tyr Arg Lys Glu Val Gly Gly Asn Tyr Ser Glu Glu Gln Lys Arg Arg
               485
                                  490
Glu Arg Asn Gln Cys Leu Gly Pro Asp Thr Arg Lys Lys Ser Glu Lys
                              505
                                                 510
          500
Val Leu Cys Lys Tyr Phe His Ser Gln Asn Leu Gln Lys Ala Val Thr 515 520 525
Thr Glu Thr Ile Arg Asp Leu Gln Pro Gly Lys Ser Tyr Leu Leu Asp
                       535
                                           540
Val Tyr Val Val Gly His Gly Gly His Ser Val Lys Tyr Gln Ser Lys
                                       555
                                                           560
                   550
Leu Val Lys Thr Arg Lys Val Cys
               565
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<210> 292

<211> 123

<212> PRT

<213> Mouse

<400> 292



55 Gly Gln Glu Phe Arg Phe Gly Ser Cys Gln Val Thr Gly Val Val Leu 70 75 Pro Glu Leu Trp Glu Ala Phe Trp Thr Val Lys Asn Thr Val Gln Thr 90 85 Gln Asp Asp Ile Thr Ser Ile Arg Leu Leu Lys Pro Gln Val Leu Arg 100 105 110 Asn Val Ser Val Ile Arg Trp Glu Gly Asp Ser · 120 115 <210> 293 <211> 66 <212> PRT <213> Mouse <400> 293 Met Asp Val Trp Ser Gly Leu Pro Leu Glu Thr Leu Trp Ile Tyr Glu 10 5 Ala Val Leu Pro Trp Leu Leu Met Gly Gln Gly His Ala Trp Val Cys 25 20 30 Gly Pro Ile Ala Leu Trp Val Phe Val Asn Val Pro Gly Leu Cys Tyr 40 35 -45 His Gln Lys Pro Phe Arg Cys Pro Trp Ser Gly Leu Leu Pro Glu Ala 55 60 50 Leu Cys 65 <210> 294 <211> 294 <212> PRT <213> Rat <400> 294 Met Thr Val Phe Arg Lys Val Thr Thr Met Ile Ser Trp Met Leu Leu 10 Ala Cys Ala Leu Pro Cys Ala Ala Asp Pro Met Leu Gly Ala Phe Ala 20 25 30 20 Arg Arg Asp Phe Gln Lys Gly Gly Pro Gln Leu Val Cys Ser Leu Pro 45 35 40 Gly Pro Gln Gly Pro Pro Gly Pro Pro Gly Ala Pro Gly Ser Ser Gly 55 60 50 Met Val Gly Arg Met Gly Phe Pro Gly Lys Asp Gly Gln Asp Gly Gln 75 70 Asp Gly Asp Arg Gly Asp Ser Gly Glu Glu Gly Pro Pro Gly Arg Thr 85 90 95 90 85 Gly Asn Arg Gly Lys Gln Gly Pro Lys Gly Lys Ala Gly Ala Ile Gly 105 . 110 100 Arg Ala Gly Pro Arg Gly Pro Lys Gly Val Ser Gly Thr Pro Gly Lys 115 120 125 His Gly Ile Pro Gly Lys Lys Gly Pro Lys Gly Lys Lys Gly Glu Pro 130 135 140 . 135 Gly Leu Pro Gly Pro Cys Ser Cys Gly Ser Ser Arg Ala Lys Ser Ala 145 150 155 160 Phe Ser Val Ala Val Thr Lys Ser Tyr Pro Arg Glu Arg Leu Pro Ile 170 175 165 Lys Phe Asp Lys Ile Leu Met Asn Glu Gly Gly His Tyr Asn Ala Ser

185



```
Ser Gly Lys Phe Val Cys Ser Val Pro Gly Ile Tyr Tyr Phe Thr Tyr
                         200
       195
Asp Ile Thr Leu Ala Asn Lys His Leu Ala Ile Gly Leu Val His Asn
   210
                     215
                                         220
Gly Gln Tyr Arg Ile Arg Thr Phe Asp Ala Asn Thr Gly Asn His Asp
                 230
                                    235
Val Ala Ser Gly Ser Thr Ile Leu Ala Leu Lys Glu Gly Asp Glu Val
245 250 255
Trp Leu Gln Ile Phe Tyr Ser Glu Gln Asn Gly Leu Phe Tyr Asp Pro
         260
                             265
                                     270
Tyr Trp Thr Asp Ser Leu Phe Thr Gly Phe Leu Ile Tyr Ala Asp Gln
                         280
      275
                                             285
Gly Asp Pro Asn Glu Val
   290
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<210> 295 <211> 243 <212> PRT . <213> Rat

<400> 295

Met Arg Pro Leu Leu Ala Leu Leu Leu Leu Gly Leu Ala Ser Gly Ser 1 5 10 15 Pro Pro Leu Asp Asp Asn Lys Ile Pro Ser Leu Cys Pro Gly Gln Pro 20 25 30. Gly Leu Pro Gly Thr Pro Gly His His Gly Ser Gln Gly Leu Pro Gly 35 40 45 Arg Asp Gly Arg Asp Gly Arg Asp Gly Ala Pro Gly Ala Pro Gly Glu
50 55 60 50 55 60 Lys Gly Glu Gly Gly Arg Pro Gly Leu Pro Gly Pro Arg Gly Glu Pro 65 70 75 80 75 Gly Pro Arg Gly Glu Ala Gly Pro Val Gly Ala Ile Gly Pro Ala Gly 90 85 Glu Cys Ser Val Pro Pro Arg Ser Ala Phe Ser Ala Lys Arg Ser Glu 100 105 110 Ser Arg Val Pro Pro Pro Ala Asp Thr Pro Leu Pro Phe Asp Arg Val 115 120 . 125 Leu Leu Asn Glu Gln Gly His Tyr Asp Ala Thr Thr Gly Lys Phe Thr 130 135 140 Cys Gln Val Pro Gly Val Tyr Tyr Phe Ala Val His Ala Thr Val Tyr 155 150 Arg Ala Ser Leu Gln Phe Asp Leu Val Lys Asn Gly Gln Ser Ile Ala 170 165 Ser Phe Phe Gln Phe Phe Gly Gly Trp Pro Lys Pro Ala Ser Leu Ser 180 185 190 Gly Gly Ala Met Val Arg Leu Glu Pro Glu Asp Gln Val Trp Val Gln 195 200 205 · Val Gly Val Gly Asp Tyr Ile Gly Ile Tyr Ala Ser Ile Lys Thr Asp 220 215 Ser Thr Phe Ser Gly Phe Leu Val Tyr Ser Asp Trp His Ser Ser Pro 235 230 Val Phe Ala

<210> 296 <211> 444 <212> PRT



<213> Rat

<400> 296 Met Leu Val Ala Phe Leu Gly Ala Ser Ala Val Thr Ala Ser Thr Gly Leu Leu Trp Lys Lys Ala His Ala Glu Ser Pro Pro Ser Val Asn Ser Lys Lys Thr Asp Ala Gly Asp Lys Gly Lys Ser Lys Asp Thr Arg Glu Val Ser Ser His Glu Gly Ser Ala Ala Asp Thr Ala Ala Glu Pro Tyr Pro Glu Glu Lys Lys Lys Arg Ser Gly Phe Arg Asp Arg Lys Val Met Glu Tyr Glu Asn Arg Ile Arg Ala Tyr Ser Thr Pro Asp Lys Ile Phe Arg Tyr Phe Ala Thr Leu Lys Val Ile Asn Glu Pro Gly Glu Thr 100 105 110 Glu Val Phe Met Thr Pro Gln Asp Phe Val Arg Ser Ile Thr Pro Asn Glu Lys Gln Pro Glu His Leu Gly Leu Asp Gln Tyr Ile Ile Lys Arg Phe Asp Gly Lys Lys Ile Ala Gln Glu Arg Glu Lys Phe Ala Asp Glu
145 150 150 160 Gly Ser Ile Phe Tyr Thr Leu Gly Glu Cys Gly Leu Ile Ser Phe Ser Asp Tyr Ile Phe Leu Thr Thr Val Leu Ser Thr Pro Gln Arg Asn Phe Glu Ile Ala Phe Lys Met Phe Asp Leu Asn Gly Asp Gly Glu Val Asp Met Glu Glu Phe Glu Gln Val Gln Ser Ile Ile Arg Ser Gln Thr Ser 210 215 Met Gly Met Arg His Arg Asp Arg Pro Thr Thr Gly Asn Thr Leu Lys Ser Gly Leu Cys Ser Ala Leu Thr Thr Tyr Phe Phe Gly Ala Asp Leu Lys Gly Lys Leu Thr Ile Lys Asn Phe Leu Glu Phe Gln Arg Lys Leu Gln His Asp Val Leu Lys Leu Glu Phe Glu Arg His Asp Pro Val Asp Gly Arg Ile Ser Glu Arg Gln Phe Gly Gly Met Leu Leu Ala Tyr Ser Gly Val Gln Ser Lys Lys Leu Thr Ala Met Gln Arg Gln Leu Lys Lys His Phe Lys Asp Gly Lys Gly Leu Thr Phe Gln Glu Val Glu Asn Phe Tyr His Met Ala Gly Ala Ser Leu Asp Lys Val Thr Met Gln Gln Val Ala Arg Thr Val Ala Lys Val Glu Leu Ser Asp His Val Cys Asp Val Val Phe Ala Leu Phe Asp Cys Asp Gly Asn Gly Glu Leu Ser Asn Lys 385 390 395 400 Glu Phe Val Ser Ile Met Lys Glm Arg Leu Met Arg Gly Leu Glu Lys Pro Lys Asp Met Gly Phe Thr Arg Leu Met Gln Ala Met Trp Lys Cys



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Ala Gln Glu Thr Ala Trp Asp Phe Ala Leu Pro Lys
       435
                          440
     <210> 297
      <211> 65
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      <213> Human
    <400> 297
Met Thr Met Leu His Leu Ala Val Ile Phe Leu Phe Ser Ala Leu Ser
                                 10
                                                    15
Arg Ala Leu Val Gln Cys Ser Ser His Arg Ala Arg Val Val Leu Ser
                              25
        20 .
                                                30
Trp Ala Asp Tyr Leu Arg Arg Val Ala Pro Thr Ala Leu Ala Thr Ala
                        40
      35
                                           45
Leu Asp Val Gly Leu Ser Asn Trp Ser Phe Leu Tyr Val Thr Val Ser
                      55
                                          60
 50
Leu
65
      <210> 298
      <211> 52
      <212> PRT
      <213> Human
     <400> 298
Met Lys Ile Asn Ile Ile Gln Gly Ser Ile Met Ile Leu Leu Ile Cys
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              5
Leu Ser Gln Thr Cys Thr Ser Leu Pro Val Gln Glu Ala Leu Ile Thr
                            25
                                                30
         20
Phe Cys His Leu Tyr Phe Thr Tyr Cys Tyr Ser Gly Asn Ser Asn Lys
      35
                        40
Met Gln Val Leu
    50
      <210> 299
      <211> 41
      <212> PRT
      <213> Human
      <400> 299
Met Pro Cys Val Leu Phe Phe Phe Phe Leu Ser Thr Ser Lys Ser
                                 10
Met Ile Tyr Ser Ser Leu Met Leu Gly Leu Tyr Ile Pro Ser Glu Ala
        20
                             25
                                                 30
Cys Val Leu Gly Leu Lys Phe Lys Phe
                          40
       35
      <210> 300
      <211> 80
      <212> PRT
      <213> Mouse
      <400> 300
Met Val Trp Gly Thr Leu Leu Gly Arg Val Leu Ala Ala Leu Leu Asn
                                 10
                                                    15
Ile Val Pro Thr Glu Ser Ser Tyr Arg Ser Pro Ser Phe Leu Ala Gly
```

```
Phe Arg Phe Cys Cys Ser Pro Trp Ser Gln His Phe Gly Cys Gly Arg
                           40
Leu Thr Ser Cys Leu Pro Pro Cys Val Asp Arg Val Val Lys Thr Tyr
                      55
Ser Ser Pro Pro Cys Leu Ser Val Asn Gly His Asp Val Thr Ile Cys
                  .70
                                       75
     <210> 301
     <211> 82
     <212> PRT
     <213> Mouse
     <400> 301
Met Gly Ser Val Leu Thr Ser Cys Phe Cys Val Gly Gly Ser Ala Glu
                                  10
Ala Trp Asn Trp Leu Pro Ser Ala Ser Ser Leu Phe Pro Cys Cys Ile
          20
                               25
Ala Thr Leu Leu Pro Leu Leu Phe Leu Leu Pro His Leu His Ser Thr
                           40
Leu Ser Arg Val Gln Arg Leu Asn Phe Asn Ile Gly His Leu Gly Val
                       55
                                          60
Tyr Leu Tyr Val Asn Asn Asp Ile Arg Ser Arg Val Thr Pro Leu Leu
                   70
                                       75
Ser Ser
     <210> 302
     <211> 411
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     <213> Rat
     <400> 302
Met Pro Thr Met Trp Pro Leu Leu His Val Leu Trp Leu Ala Leu Val
                                 10
Cys Gly Ser Val His Thr Thr Leu Ser Lys Ser Asp Ala Lys Lys Ala
          20
                               25
Ala Ser Lys Thr Leu Leu Glu Lys Thr Gln Phe Ser Asp Lys Pro Val
       35
                            40
                                              45
Gln Asp Arg Gly Leu Val Val Thr Asp Ile Lys Ala Glu Asp Val Val
                      55
                                          60
Leu Glu His Arg Ser Tyr Cys Ser Ala Arg Ala Arg Glu Arg Asn Phe
                   70
                                       75
Ala Gly Glu Val Leu Gly Tyr Val Thr Pro Trp Asn Ser His Gly Tyr
                                 90
              85
Asp Val Ala Lys Val Phe Gly Ser Lys Phe Thr Gln Ile Ser Pro Val
           100
                               105
                                                . 110
Trp Leu Gln Leu Lys Arg Arg Gly Arg Glu Met Phe Glu Ile Thr Gly
      115
                           120
                                               125
Leu His Asp Val Asp Gln Gly Trp Met Arg Ala Val Lys Lys His Ala
130 135 140
Lys Gly Val Arg Ile Val Pro Arg Leu Leu Phe Glu Asp Trp Thr Tyr
                  150
                                      155
Asp Asp Phe Arg Ser Val Leu Asp Ser Glu Asp Glu Ile Glu Glu Leu
                                  170
              165
                                                      175
Ser Lys Thr Val Val Gln Val Ala Lys Asn Gln His Phe Asp Gly Phe
```

185



```
Val Val Glu Val Trp Ser Gln Leu Leu Ser Gln Lys His Val Gly Leu
      195
                         200
                                            205
Ile His Met Leu Thr His Leu Ala Glu Ala Leu His Gln Ala Arg Leu
                    215
  210
                                       220
Leu Val Ile Leu Val Ile Pro Pro Ala Val Thr Pro Gly Thr Asp Gln
                  230
                                    235
Leu Gly Met Phe Thr His Lys Glu Phe Glu Gln Leu Ala Pro Ile Leu
            245
                              250
Asp Gly Phe Ser Leu Met Thr Tyr Asp Tyr Ser Thr Ser Gln Gln Pro
                            265
                                               270
Gly Pro Asn Ala Pro Leu Ser Trp Ile Arg Ala Cys Val Gln Val Leu
      275
                280
Asp Pro Lys Ser Gln Trp Arg Ser Lys Ile Leu Leu Gly Leu Asn Phe 290 295 300
Tyr Gly Met Asp Tyr Ala Ala Ser Lys Asp Ala Arg Glu Pro Val Ile
                 310
                                   315
Gly Ala Arg Ala Val Leu Lys Val Ala Leu Pro Leu Ala Val Ser Ser
             325
                               330
                                                   335
Gln Gln Ile Trp Thr Leu Gly Arg Gly Gly Ser Thr Ser Ala Leu Leu
         340
                            345
                                     350
Leu Ala Gly Leu Gly Leu Ala Ser Glu Pro Cys Thr Lys Ser Glu Glu
      355 360 365
Val Pro Lys Lys Ser Leu Leu Asp Thr Val Trp His Trp Gln Gly Glu
                   375
                                       380
Pro Gly Ala Leu Cys Arg Gly Arg Leu His Thr Trp Ile Leu Val Ser
                390
                                   395
Ala Val Pro Gln Ala Cys Thr Cys Leu Phe Gln
             405
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<213> Mouse

<400> 303

Met Gly Ser Pro Arg Leu Ala Ala Leu Leu Ser Leu Pro Leu Leu 1 5 10 Leu Ile Gly Leu Ala Val Ser Ala Arg Val Ala Cys Pro Cys Leu Arg 20 25 30 Ser Trp Thr Ser His Cys Leu Leu Ala Tyr Arg Val Asp Lys Arg Phe 35 40 45 Ala Gly Leu Gln Trp Gly Trp Phe Pro Leu Leu Val Arg Lys Ser Lys 55 60 Ser Pro Pro Lys Phe Glu Asp Tyr Trp Arg His Arg Thr Pro Ala Ser 70 75 Phe Gln Arg Lys Leu Leu Gly Ser Pro Ser Leu Ser Glu Glu Ser His 90 Arg Ile Ser Ile Pro Ser Ser Ala Ile Ser His Arg Gly Gln Arg Thr 100 105 110 Lys Arg Ala Gln Pro Ser Ala Ala Glu Gly Arg Glu His Leu Pro Glu 115 120 125 Ala Gly Ser Gln Lys Cys Gly Gly Pro Glu Phe Ser Phe Asp Leu Leu 130 135 140 Pro Glu Val Gln Ala Val Arg Val Thr Ile Pro Ala Gly Pro Lys Ala 150 155 Ser Val Arg Leu Cys Tyr Gln Trp Ala Leu Glu Cys Glu Asp Leu Ser 165 , 170



| Ser | Pro | Phie | Asp 180 | Thr | Gln | Lys | Ile | Val 185 | Ser | G1y | Gly | His | Thr 190 | Val | Asp |
|------------|------------|------------|------------|-----|------------|------------|------------|------------|-----|------------|------------|-------------------|------------|-----|------------|
| Leu | Pro | Tyr 195 | Glu | Phe | Leu | Leu | Pro 200 | Cys | Met | Суѕ | Ile | Glu 205 | Ala | Ser | Tyr |
| Leu | Gln 210 | Glu | Asp | Thr | Val | Arg 215 | Arg | Lys | Lys | Cys | Pro 220 | Phe | Gln | Ser | Trp |
| Pro 225 | 'Glu | Ala | Tyr | Gly | Ser 230 | Asp | Phe | Trp | Gln | Ser 235 | Ile | Arg | Phe | Thr | Asp 240 |
| _ | | | | 245 | | | | | 250 | | | Leu | | 255 | |
| | _ | | 260 | | | | | 265 | | | | Pro | 270 | | |
| _ | | 275 | | | | | 280 | | | | | Glu 285 | - | _ | _ |
| | 290 | | | | | 295 | | | | | 300 | Phe | | | |
| 305 | | • | | | 310 | | | | | 315 | | Ser | | | 320 |
| | | _ | | 325 | | | _ | | 330 | | | Gln | | 335 | |
| | | | 340 | _ | | _ | | 345 | | | | Ala | 350 | | _ |
| | | 355 | | | | | 360 | | | | | Tyr 365 | | | |
| | 370 | | _ | | | 375 | | | | | 380 | Ile | | | |
| 385 | _ | | | | 390 | | | | | 395 | | Asp | | | 400 |
| | | _ | | 405 | | | | | 410 | | | Tyr | | 415 | |
| | | | 420 | | | • | | 425 | | | | Pro | 430 | | |
| | | 435 | • | | | • | 440 | | | | | Val 445 Asp | | | |
| | 450 | | | - | | 455 | | | _ | | 460 | Pro | | | |
| 465 | | _ | | | 470 | | | | - | 475 | | Gly | | | 480 |
| | | | | 485 | | | | | 490 | | | Ser | | 495 | |
| | | | 500 | | | | | 505 | | | | Pro | 510 | | |
| | | 515 | | | | | 520 | | | | | 525 | | | Arg |
| | 530 | | | | | 535 | | | | | 540 | Asp | | | |
| 545 | | _ | | | 550 | | | | | 555 | | Ala | | | 560 |
| | | _ | | 565 | | | | | 570 | | | Leu | | 575 | |
| • | | | 580 | | | | | 585 | | | | Gln | 590 | | |
| | | 595 Pro | | | | | 600 | _ | - | - | • | 605 | _ | | |
| | 610 | | 4 - | 4 | | 615 | - | | | | | | | | |



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Val Asn Leu Thr Glu Leu Ser Leu Val Arg Asn Ser Leu Thr Ala Ala 225 230 235

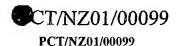
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Asn His Ile Asn Arg Val Pro Pro Asn Ala Phe Ser Tyr Leu Arg Gln 265

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255 ·

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Leu Tyr Arg Leu Asp Met Ser Asn Asn Asn Leu Ser Asn Leu Pro Gln
       275
                         280
Gly Ile Phe Asp Asp Leu Asp Asn Ile Thr Gln Leu Ile Leu Arg Asn
   290
                     295
                                        300
Asn Pro Trp Tyr Cys Gly Cys Lys Met Lys Trp Val Arg Asp Trp Leu 305 310 315
                 310
                                    315
Gln Ser Leu Pro Val Lys Val Asn Val Arg Gly Leu Met Cys Gln Ala
325 330 335
Pro Glu Lys Val Arg Gly Met Ala Ile Lys Asp Leu Ser Ala Glu Leu 340 . 345 . 350
Phe Asp Cys Lys Asp Ser Gly Ile Val Ser Thr Ile Gln Ile Thr Thr
                                   365
                 360
      355
Ala Ile Pro Asn Thr Ala Tyr Pro Ala Gln Gly Gln Trp Pro Ala Pro 370 375 380
          375
   370
                                        380
Val Thr Lys Gln Pro Asp Ile Lys Asn Pro Lys Leu Ile Lys Asp Gln
         390
                                   395
Arg Thr Thr Gly Ser Pro Ser Arg Lys Thr Ile Leu Ile Thr Val Lys
              405
                                410
                                                  415
Ser Val Thr Pro Asp Thr Ile His Ile Ser Trp Arg Leu Ala Leu Pro
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                           425
                                             430
Met Thr Ala Leu Arg Leu Ser Trp Leu Lys Leu Gly His Ser Pro Ala
                        440
                                            445
       435
Phe Gly Ser Ile Thr Glu Thr Ile Val Thr Gly Glu Arg Ser Glu Tyr
 450
                    455
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Leu Val Thr Ala Leu Glu Pro Glu Ser Pro Tyr Arg Val Cys Met Val
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Pro Met Glu Thr Ser Asn Leu Tyr Leu Phe Asp Glu Thr Pro Val Cys
                                 490 .
Ile Glu Thr Gln Thr Ala Pro Leu Arg Met Tyr Asn Pro Thr Thr
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          500
Leu Asn Arg Glu Gln Glu Lys Glu Pro Tyr Lys Asn Pro Asn Leu Pro
       515
                         520
                                           525
Leu Ala Ala Ile Ile Gly Gly Ala Val Ala Leu Val Ser Ile Ala Leu
   530
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                                        540
Leu Ala Leu Val Cys Trp Tyr Val His Arg Asn Gly Ser Leu Phe Ser 545 550 560
Arg Asn Cys Ala Tyr Ser Lys Gly Arg Arg Arg Lys Asp Asp Tyr Ala
             565 570 575
Glu Ala Gly Thr Lys Lys Asp Asn Ser Ile Leu Glu Ile Arg Glu Thr
                           585
                                                590
          580
Ser Phe Gln Met Leu Pro Ile Ser Asn Glu Pro Ile Ser Lys Glu Glu
      595
                        600
                                           605
Phe Val Ile His Thr Ile Phe Pro Pro Asn Gly Met Asn Leu Tyr Lys
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Asn Asn Leu Ser Glu Ser Ser Ser Asn Arg Ser Tyr Arg Asp Ser Gly
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Ile Pro Asp Ser Asp His Ser His Ser
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      <213> Rat
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Gly Leu Ala Gly Ala Leu Pro Thr Leu Gly Pro Gly Trp Arg Arg Gln
                          40
Asn Pro Glu Pro Pro Ala Ser Arg Thr Arg Ser Leu Leu Leu Asp Ala
                      55
                                         60
Ala Ser Gly Gln Leu Arg Leu Glu Tyr Gly Phe His Pro Asp Ala Val
                  70
                                      75
Ala Trp Ala Asn Leu Thr Asn Ala Ile Arg Glu Thr Gly Trp Ala Tyr
                                 90
              85
Leu Asp Leu Gly Thr Asn Gly Ser Tyr Lys Trp Ile Pro Arg Ala Ala
                          105
         100
Gly Leu Cys Ser Trp Cys Gly Gly Gly Leu Cys Val Arg Gly Ala His
115 120 125
Leu His Ala Leu Asp Glu His Gly Gly Gln Leu Leu Arg Pro Leu Arg
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Val Arg Ser Arg Leu Leu
1.45
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255

. 250



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Lys Lys Asp Trp Ser Leu Phe Arg Met Phe Ser Arg Thr Leu Thr Glu
                            265
                                             270
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Ala Cys Pro Leu Ala Ser Gln Ser Leu Val Tyr Val Asp Ile Thr Gly
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                        280
                                           285
Tyr Ser Gln Asp Asn Glu Thr Leu Glu Val Ser Pro Pro Pro Thr Ser
                    295
   290
                                      300
Thr Tyr Gln Asp Val Ile Leu Gly Thr Arg Lys Thr Tyr Ala Val Tyr 305 310 315 320
Asp Leu Phe Asp Thr Ala Met Ile Asn Asn Ser Arg Asn Leu Asn Ile
             325
                         330
                                         335 .
Gln Leu Lys Trp Lys Arg Pro Pro Asp Asn Glu Ala Leu Pro Val Pro
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Phe Leu His Ala Gln Arg Tyr Val Ser Gly Tyr Gly Leu Gln Lys Gly 355 360 365
            360
                                          365
       355
Glu Leu Ser Thr Leu Leu Tyr Asn Ser His Pro Tyr Arg Ala Phe Pro
                    375
                                     380
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Val Leu Leu Asp Ala Val Pro Trp Tyr Leu Arg Leu Tyr Val His
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                                   395
Thr Leu Thr Ile Thr Ser Lys Gly Lys Asp Asn Lys Pro Ser Tyr Ile
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                               410
His Tyr Gln Pro Ala Gln Asp Arg Gln Gln Pro His Leu Leu Glu Met
          420
                            425
                                             430
Leu Ile Gln Leu Pro Ala Asn Ser Val Thr Lys Val Ser Ile Gln Phe
                        440
Glu Arg Ala Leu Leu Lys Trp Thr Glu Tyr Thr Pro Asp Pro Asn His
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                                       460
Gly Phe Tyr Val Ser Pro Ser Val Leu Ser Ala Leu Val Pro Ser Met 465 470 475 480
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Val Ala Ala Lys Pro Val Asp Trp Glu Glu Ser Pro Leu Phe Asn Thr
485 490 495
Leu Phe Pro Val Ser Asp Gly Ser Ser Tyr Phe Val Arg Leu Tyr Thr
                 505
                                              510
          500
Glu Pro Leu Leu Val Asn Leu Pro Thr Pro Asp Phe Ser Met Pro Tyr
               520
                                        525
      515
Asn Val Ile Cys Leu Thr Cys Thr Val Val Ala Val Cys Tyr Gly Ser
 530
                     535
                                       540
Phe Tyr Asn Leu Leu Thr Arg Thr Phe His Ile Glu Glu Pro Lys Ser
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Gly Gly Leu Ala Lys Arg Leu Ala Asn Leu Ile Arg Arg Ala Arg Gly
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Val Pro Pro Leu
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Leu Gln Ser Val Phe Val Gln Ser Tyr Leu Asp Gln Gly Thr Gln Ile
                                 45
      35
                         40
Phe Leu Asn Asn Ser Ile Glu Lys Ser Gly Trp Leu Phe Ile Gln Leu
                                        60
    50
                      55
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Tyr His Ser Phe Val Ser Ser Val Phe Ser Leu Phe Met Ser Arg Thr
                70
                                  75
Ser Ile Asn Gly Leu Leu Gly Arg Gly Ser Met Phe Val Phe Ser Pro
            85
                              90
                                             95
Asp Gln Phe Gln Arg Leu Leu Lys Ile Asn Pro Asp Trp Lys Thr His
         100
                          105
                                           110 .
Arg Leu Leu Asp Leu Gly Ala Gly Asp Gly Glu Val Thr Lys Ile Met
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    11.5
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Ser Pro His Phe Glu Glu Ile Tyr Ala Thr Glu Leu Ser Glu Thr Met
                    135
  130
                                     140
Ile Trp Gln Leu Gln Lys Lys Lys Tyr Arg Val Leu Gly Ile Asn Glu
               150
                        155
Trp Gln Asn Thr Gly Phe Gln Tyr Asp Val Ile Ser Cys Leu Asn Leu
            165 170
Leu Asp Arg Cys Asp Gln Pro Leu Thr Leu Leu Lys Asp Ile Arg Ser
                  185 . 190
Val Leu Glu Pro Thr Gln Gly Arg Val Ile Leu Ala Leu Val Leu Pro
      195
                      200
                                       205
Phe His Pro Tyr Val Glu Asn Val Gly Gly Lys Trp Glu Lys Pro Ser
           215
                                 220
 210
Glu Ile Leu Glu Ile Lys Gly Gln Asn Trp Glu Glu Gln Val Asn Ser
               230 235
225
Leu Pro Glu Val Phe Arg Lys Ala Gly Phe Val Ile Glu Ala Phe Thr
                             250
            245
                                               255
Arg Leu Pro Tyr Leu Cys Glu Gly Asp Met Tyr Asn Asp Tyr Tyr Val
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       260
                                            270
Leu Asp Asp. Ala Val Phe Val Leu Arg Pro Val
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                        280
     <210> 309
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     <213> Rat
     <400> 309
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Phe Phe Pro Val Lys Thr Val Ala Leu Glu Glu Ile Ser Thr Ile Cys
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                           25
Arg Ala Asp Val Leu
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     <213> Mouse
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Met Ala Ala Ser Trp Gly Gln Val Leu Ala Leu Val Leu Val Ala Ala
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Leu Trp Gly Gly Thr Gln Pro Leu Leu Lys Arg Ala Ser Ser Gly Leu
                          25
         20
Glu Gln Val Arg Glu Arg Thr Trp Ala Trp Gln Leu Leu Gln Glu Ile
                        40
    . 35
Lys Ala Leu Phe Gly Asn Thr Glu Val Arg Leu Ala Leu Thr Asp Glu
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                                     60
Pro Leu Lys Ile Ser Pro
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65

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     <211> 58
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Met Leu Leu Ser Ser Leu Val Ser Leu Ala Gly Ser Val Tyr Leu Ala
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Trp Ile Leu Phe Phe Val Leu Tyr Asp Phe Cys Ile Val Cys Ile Thr
                  25
                                            30
      20
Thr Tyr Ala Ile Asn Val Ser Leu Met Trp Leu Ser Phe Arg Lys Val
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Gln Glu Pro Gln Gly Lys Ala Lys Arg His
  50
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     <210> 312
     <211> 52
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Met Gly Thr Pro Gln Gly Glu Asn Trp Leu Ser Trp Met Phe Glu Lys
             5
1
                               10
                                          . 15
Leu Val Val Wat Wat Cys Tyr Phe Ile Leu Ser Ile Ile Asn Ser
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                                    30
Met Ala Gln Ser Tyr Ala Lys Arg Ile Gln Gln Arg Leu Asn Ser Glu
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Glu Lys Thr Lys
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1
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                                                15
Leu Lys Trp Cys Ala Trp Val Ala Val Tyr Cys Ser Phe Ile Ser Phe
     20
                         25
                                           30
Ala Asn Ser Arg Ser Ser Glu Asp Thr Lys Gln Met Met Ser Ser Phe
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Pro Met Thr Pro Pro Trp
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<213> Rat

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Lys Glu Lys Pro Ser Tyr Asp Thr Glu Ala Asp Pro Ser Glu Gly Leu 180

Met Asn Val Leu Lys Lys Ile Tyr Glu Asp Gly Asp Asp Asp Met Lys 195

Lys Lys Ile Tyr Glu Asp Gly Asp Asp Asp Met Lys 200

Asn Thr Arg Trp Asp Tyr Leu Thr Gln Val Glu Lys Glu Cys Lys Glu

Arg Thr Ile Asn Lys Ala Trp Val Glu Ser Arg Glu Lys Gln Ala Arg 210 215 220

Glu Asp Thr Glu Phe

225

<210> 316

<211> 128

<212> PRT

<213> Rat

<400> 316

Arg Ala Glu Phe Gly Thr Ser Gly Glu Met Gly Asn Ala Ala Leu Gly

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Ala Glu Leu Gly Val Arg Val Leu Leu Phe Val Ala Phe Leu Ala Thr
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Glu Leu Leu Pro Pro Phe Gln Arg Arg Ile Gln Pro Glu Glu Leu Trp
35 40 45

Leu Tyr Arg Asn Pro Tyr Val Glu Ala Glu Tyr Phe Pro Thr Gly Pro



55 60 Met Phe Val Ile Ala Phe Leu Thr Pro Leu Ser Leu Ile Phe Phe Ala 70 75 Lys Phe Leu Arg Lys Ala Asp Ala Thr Asp Ser Lys Gln Ala Cys Leu 90 85 Ala Ala Ser Leu Ala Leu Ala Leu Asn Gly Val Phe Thr Asn Ile Ile
100 , 105 110 Lys Leu Ile Val Gly Arg Pro Arg Pro Asp Phe Phe Tyr Arg Cys Phe 115 120 125 <210> 317 <211> 75 <212> PRT <213> Rat <400> 317 Ser Ala Gly Val Met Thr Ala Ala Val Phe Phe Gly Cys Ala Phe Ile 5 10 Ala Phe Gly Pro Ala Leu Ser Leu Tyr Val Phe Thr Ile Ala Thr Asp 20 25 30 Pro Leu Arg Val Ile Phe Leu Ile Ala Gly Ala Phe Phe Trp Leu Val 35 40 45 Ser Leu Leu Ser Ser Val Phe Trp Phe Leu Val Arg Val Ile Thr 50 - 55 Asp Asn Arg Asp Gly Pro Val Gln Asn Tyr Leu 70 <210> 318 <211> 43 <212> PRT <213> Human <400> 318 Met Lys Leu Ser Gly Met Phe Leu Leu Ser Leu Ala Leu Phe Cys 10 Phe Leu Thr Gly Val Phe Ser Gln Gly Gly Gln Val Asp Cys Gly Glu 20 25 30 . 25 Ser Arg Thr Pro Arg Pro Thr Ala Leu Gly Asn 35 40 <210> 319 <211> 86 <212> PRT <213> Mouse <400> 319 Met Leu Gln Gly Pro Ala Pro Ser Cys Phe Trp Val Phe Ser Gly Ile 15 5 10 Cys Val Phe Trp Asp Phe Ile Phe Ile Ile Phe Phe Asn Val Leu Ser 20 25 Leu Gly Asn Arg Glu Ile Ser Ala Lys Asp Phe Ala Asp Gln Pro Ala 35 40 45 Gly Ala Gln Gly Met Trp Gly Ile Trp Gly His Thr Ile Thr Cys Gly 55 60 Leu Ala Pro Gly Ala Lys Pro Cys Ser Leu Lys Arg Glu Gly Pro Asp 70 80

Leu Leu Ser Phe Pro Pro

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<400> 321

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<400> 322

 Arg
 Leu
 Gln
 Val
 Asp
 Thr
 Ser
 Gly
 Ser
 Lys
 Val
 Leu
 Phe
 Leu
 Phe
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 Dhe
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 Phe
 Gly
 Phe
 Gly</th

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          20
Val Phe Ala Ile Phe Met Ala Ala Glu Thr Phe Thr Asp Ile Phe Ile 35 40 45
Ser Trp Ser Gly Pro Arg Ile Gly Arg Pro Trp Gly Trp Glu Gly Pro
             55
                                      60
 50
His His His His Leu Ala Ser Gly Ser His Lys Pro Leu Pro Leu
                                   75
                70
Leu Thr His Arg Phe Pro Phe Tyr Tyr Glu Phe Lys Met Ala Phe Val
             85 90
                                                 95
Leu Trp Leu Leu Ser Pro Tyr Thr Lys Gly Ala Ser Leu Leu Tyr Arg
          100
Lys Phe Val His Pro Ser Leu Ser Arg His Glu Lys Glu Ile Asp Ala
               120
                                         125
      115
Cys Ile Val Gln Ala Lys Glu Arg Ser Tyr Glu Thr Met Leu Ser Phe
  130
                    135
                                       140
Gly Lys Arg Ser Leu Asn Ile Ala Ala Ser Ala Ala Val Gln Ala Ala
                150
                                  155
Thr Lys Ser Gln Gly Ala Leu Ala Gly Arg Leu Arg Ser Phe Ser Met
165 170 175
                               170
      165
Gln Asp Leu Arg Ser Ile Pro Asp Thr Pro Val Pro Thr Tyr Gln Asp
                            185
                                 190
         180
Pro Leu Tyr Leu Glu Asp Gln Val Pro Arg Arg Arg Pro Pro Ile Gly
      195
                        200
                                          205
Tyr Arg Pro Gly Gly Leu Gln Gly Ser Asp Thr Glu Asp Glu Cys Trp
                    215
                                      220
Ser Asp Asn Glu Ile Val Pro Gln Pro Pro Val Gly Pro Arg Glu Lys
                         235
                 230
Pro Leu Gly Arg Ser Gln Ser Leu Arg Val Val Lys Arg Lys Pro Leu
                                                  255
             245
                              250
Thr Arg Glu Gly Thr Ser Arg Ser Leu Lys Val Arg Thr Pro Lys Lys
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Ala Met Pro Ser Asp Met Asp Ser
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       275
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<400> 324



Trp Ala Val Ala Gln Arg Asp Ser Val Asp Ala Ile Gly Met Phe Leu 55 60 Gly Gly Leu Val Ala Thr Ile Phe Leu Asp Ile Ile Tyr Ile Ser Ile 70 75 Phe Tyr Ser Ser Val Ala Val Gly Asp Thr Gly Arg Phe Ser Ala Gly 90 85 Met Ala Ile Phe Ser Leu Leu Leu Lys Pro Phe Ser Cys Cys Leu Val 105 100 110 Tyr His Met His Arg Glu Arg Gly Gly Glu Leu Pro Leu Arg Ser Asp 120 Phe Phe Gly Pro Ser Gln Glu His Ser Ala Tyr Gln Thr Ile Asp Ser 135 140 Ser Asp Ser Pro Ala Asp Pro Leu Ala Ser Leu Glu Asn Lys Gly Gln 150 155 Ala Ala Pro Arg Gly Tyr 165 <210> 325 <211> 338 <212> PRT <213> Rat <400> 325 Ile Arg His Glu Ala Glu Ala Gly Arg His Gln Pro Glu Gln Leu Ala 1 . 5 10 Ala Asp Ser Arg Thr Glu Thr Val Gly Pro Arg Gln Ser Asn Gly Leu 20 25 Thr Gly Pro Gly Leu Pro Thr Trp Gln Leu His Pro Val Leu Phe Pro 35 40 45 Glu Leu Val Leu Trp Val Asn Met Val Pro Cys Phe Leu Leu Ser Leu 50 55 60 Leu Leu Val Arg Pro Ala Pro Val Val Ala Tyr Ser Val Ser Leu 70 75 Pro Ala Ser Phe Leu Glu Glu Val Ala Gly Ser Gly Glu Ala Glu Gly · 85 90 Ser Ser Ala Ser Ser Pro Ser Leu Leu Pro Pro Arg Thr Pro Ala Phe 100 105 110 Ser Pro Thr Pro Gly Arg Thr Gln Pro Thr Ala Pro Val Gly Pro Val .115 120 125 Pro Pro Thr Asn Leu Leu Asp Gly Ile Val Asp Phe Phe Arg Gln Tyr 130 135 140 Val Met Leu Ile Ala Val Val Gly Ser Leu Thr Phe Leu Ile Met. Phe 155 150 Ile Val Cys Ala Ala Leu Ile Thr Arg Gln Lys His Lys Ala Thr Ala 165 170 175 Tyr Tyr Pro Ser Ser Phe Pro Glu Lys Lys Tyr Val Asp Gln Arg Asp 180 185 ... 190 Arg Ala Gly Gly Pro His Ala Phe Ser Glu Val Pro Asp Arg Ala Pro . 195 . 200 205 Asp Ser Arg Gln Glu Glu Gly Leu Asp Ser Ser Gln Gln Leu Gln Ala 215 220 Asp Ile Leu Ala Ala Thr Gln Asn Leu Arg Ser Pro Ala Arg Ala Leu . 225 230 235 240 Pro Gly Ser Gly Glu Gly Thr Lys Gln Val Lys Gly Gly Ser Glu Glu 255 245 250 Glu Glu Glu Lys Glu Glu Glu Val Phe Ser Gly Gln Glu Glu Pro Arg 260 265



Glu Ala Pro Val Cys Gly Val Thr Glu Glu Lys Pro Glu Val Pro Asp
275
Glu Thr Ala Ser Ala Glu Ala Glu Gly Val Pro Ala Ala Ser Glu Gly
290
Cln Gly Glu Pro Glu Gly Ser Phe Ser Leu Ala Gln Glu Pro Gln Gly
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Ala Ala Gly Pro Ser Glu Arg Ser Cys Ala Cys Asn Arg Ile Ser Pro
325
Asn Val

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<213> Human

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Pro Gln Lys Glu Phe Ser Ile Pro Arg Ala His Ala Trp Pro Ser Pro
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                                330
Tyr Lys Asp Tyr Glu Val Lys Lys Glu Gly Ser
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     <211> 141
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Arg Gln Glu Pro Met Trp Glu Phe Asn Phe Lys Phe Lys Gln Ser
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                             25
                                               30
Pro Arg Leu Lys Ser Lys Cys Thr Gly Gly Leu Gln Pro Pro Val Gln
      35
                         40
                                            45
Tyr Glu Asp Val His Thr Asn Pro Asp Gln Asp Cys Cys Leu Leu Gln
  50
                   . 55
                                        60
Val Thr Thr Leu Asn Phe Ile Phe Ile Pro Ile Val Met Gly Met Ile
               70
                                   75
Phe Thr Leu Phe Thr Ile Asn Val Ser Thr Asp Met Arg His His Arg
                               90
             85
Val Arg Leu Val Phe Gln Asp Ser Pro Val His Gly Gly Arg Lys Leu
         100
                            105
                                            110
Arg Ser Glu Gln Gly Val Gln Val Ile Leu Asp Gln Cys Thr Ala Phe
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Gly Ser Leu Thr Gly Gly Ile Leu Ser Thr His Ser Pro
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Cys Cys Cys Leu His Ser Gly Gly Leu Gly Gly Val Pro Leu Pro Pro
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                             25
                                               30
Phe Pro Pro Gln Ala Gln Arg Gly Glu Gly Pro Gly Lys Trp Met Ser
                        40
    35
Pro Pro Leu Pro Pro His Pro Val Val Ala Pro Pro Thr Pro Ser Pro
                     55
Ser Arg Gly Cys Val Leu Leu
     <210> 329
     <211> 109
     <212> PRT
     <213> Human
     <400> 329
Asp Gly Pro Ser Pro Lys Leu Ala Leu Trp Leu Pro Ser Pro Ala Pro
                                 10
                                                  .15
Thr Ala Ala Pro Thr Ala Leu Gly Glu Ala Gly Leu Ala Glu His Ser
           20
                             25
```



Gln Arg Asp Asp Arg Trp Leu Leu Val Ala Leu Leu Val Pro Thr Cys 40 Val Phe Leu Val Val Leu Leu Ala Leu Gly Ile Val Tyr Cys Thr Arg 50 55 Cys Gly Pro His Ala Pro Asn Lys Arg Ile Thr Asp Cys Tyr Arg Trp 70 75 Val Ile His Ala Gly Ser Lys Ser Pro Thr Glu Pro Met Pro Pro Arg 85 90 Gly Ser Leu Thr Gly Val Gln Thr Cys Arg Thr Ser Val 100 105 <210> 330 <211> 155 <212> PRT <213> Human <400> 330 Ser Val Met Ala Ala Gly Leu Phe Gly Leu Ser Ala Arg Arg Leu Leu Ala Ala Ala Thr Arg Gly Leu Pro Ala Ala Arg Val Arg Trp Glu 20 25 Ser Ser Phe Ser Arg Thr Val Val Ala Pro Ser Ala Val Ala Gly Lys 40 Arg Pro Pro Glu Pro Thr Thr Pro Trp Gln Glu Asp Pro Glu Pro Glu 55 60 Asp Glu Asn Leu Tyr Glu Lys Asn Pro Asp Ser His Gly Tyr Asp Lys 70 75 Asp Pro Val Leu Asp Val Trp Asn Met Arg Leu Val Phe Phe Gly 90 95 Val Ser Ile Ile Leu Val Leu Gly Ser Thr Phe Val Ala Tyr Leu Pro 100 105 110 Asp Tyr Arg Met Lys Glu Trp Ser Arg Arg Glu Ala Glu Arg Leu Val 115 120 125 Lys Tyr Arg Glu Ala Asn Gly Leu Pro Ile Met Glu Ser Asn Cys Phe 130 135 Asp Pro Ser Lys Ile Gln Leu Pro Glu Asp Glu 145 150

<210> 331 <211> 299 <212> PRT

<213> Human

<400> 331

Met Gly Thr Lys Ala Gln Val Glu Arg Lys Leu Leu Cys Leu Phe Ile 5 10 Leu Ala Ile Leu Leu Cys Ser Leu Ala Leu Gly Ser Val Thr Val His 20 25 Ser Ser Glu Pro Glu Val Arg Ile Pro Glu Asn Asn Pro Val Lys Leu 35 40 Ser Cys Ala Tyr Ser Gly Phe Ser Ser Pro Arg Val Glu Trp Lys Phe 55 60 Asp Gln Gly Asp Thr Thr Arg, Leu Val Cys Tyr Asn Asn Lys Ile Thr 70 75 Ala Ser Tyr Glu Asp Arg Val Thr Phe Leu Pro Thr Gly Ile Thr Phe 85 90 Lys Ser Val Thr Arg Glu Asp Thr Gly Thr Tyr Thr Cys Met Val Ser

```
100 .
                             105
Glu Glu Gly Gly Asn Ser Tyr Gly Glu Val Lys Val Lys Leu Ile Val
                         120
                                          . 125
Leu Val Pro Pro Ser Lys Pro Thr Val Asn Ile Pro Ser Ser Ala Thr
   130
                     135
                                       140
Ile Gly Asn Arg Ala Val Leu Thr Cys Ser Glu Gln Asp Gly Ser Pro
145
               150
                           155
Pro Ser Glu Tyr Thr Trp Phè Lys Asp Gly Ile Val Met Pro Thr Asn
             165
                               170
Pro Lys Ser Thr Arg Ala Phe Ser Asn Ser Ser Tyr Val Leu Asn Pro
         180
                          185
                                          190
Thr Thr Gly Glu Leu Val Phe Asp Pro Leu Ser Ala Ser Asp Thr Gly
195 200 205
      195
                       200
                                           205
Glu Tyr Ser Cys Glu Ala Arg Asn Gly Tyr Gly Thr Pro Met Thr Ser 210 215 220 .
   210
Asn Ala Val Arg Met Glu Ala Val Glu Arg Asn Val Gly Val Ile Val
225
                 230
                                    235
Ala Ala Val Leu Val Thr Leu Ile Leu Leu Gly Ile Leu Val Phe Gly
            245 250 255
Ile Trp Phe Ala Tyr Ser Arg Gly His Phe Asp Arg Thr Lys Lys Gly 260 265 270
Thr Ser Ser Lys Lys Val Ile Tyr Ser Gln Pro Ser Ala Arg Ser Glu
                        280
Gly Glu Phe Lys Gln Thr Ser Ser Phe Leu Val
                      295
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<210> 332 <211> 299 <212> PRT <213> Mouse

<400> 332

Ala Arg Ala Gly Ala Cys Tyr Cys Pro Ala Gly Phe Leu Gly Ala Asp . 10 Cys Ser Leu Ala Cys Pro Gln Gly Arg Phe Gly Pro Ser Cys Ala His . 20 25 30 Val Cys Thr Cys Gly Gln Gly Ala Ala Cys Asp Pro Val Ser Gly Thr 40 Cys Ile Cys Pro Pro Gly Lys Thr Gly Gly His Cys Glu Arg Gly Cys 55 Pro Gln Asp Arg Phe Gly Lys Gly Cys Glu His Lys Cys Ala Cys Arg 70 Asn Gly Gly Leu Cys His Ala Thr Asn Gly Ser Cys Ser Cys Pro Leu 85 90 95 85 90 95 Gly Trp Met Gly Pro His Cys Glu His Ala Cys Pro Ala Gly Arg Tyr 105 100 110 Gly Ala Ala Cys Leu Leu Glu Cys Ser Cys Gln Asn Asn Gly Ser Cys 115 120 .125 Glu Pro Thr Ser Gly Ala Cys Leu Cys Gly Pro Gly Phe Tyr Gly Gln 130 135 140

150 155 Arg Val Cys Glu Cys Gln Gln Gly Ala Pro Cys Asp Pro Val Ser Gly 165 170 175 Arg Cys Leu Cys Pro Ala Gly Phe Arg Gly Gln Phe Cys Glu Arg Gly 180 185

Ala Cys Glu Asp Thr Cys Pro Ala Gly Phe His Gly Ser Gly Cys Gln

Cys Lys Pro Gly Phe Phe Gly Asp Gly Cys Leu Gln Gln Cys Asn Cys



195 200 205 Pro Thr Gly Val Pro Cys Asp Pro Ile Ser Gly Leu Cys Leu Cys Pro 210 215 220 Pro Gly Arg Ala Gly Thr Thr Cys Asp Leu Asp Cys Arg Arg Gly Arg 230 235 Phe Gly Pro Gly Cys Ala Leu Arg Cys Asp Cys Gly Gly Gly Ala Asp 245 250 255 245 250 255 Cys Asp Pro Ile Ser Gly GIn Cys His Cys Val Asp Ser Tyr Thr Gly 260 265 270 Pro Thr Cys Arg Glu Val Pro Thr Gln Leu Ser Ser Ile Arg Pro Ala 275 280 Pro Gln His Ser Ser Ser Lys Ala Met Lys His 295

<210> 333

<211> 109

<212> PRT

<213> Mouse

<400> 333

Gly Thr Arg Val Gly Thr Pro Tyr Tyr Met Ser Pro Glu Arg Ile His 10 Glu Asn Gly Tyr Asn Phe Lys Ser Asp Ile Trp Ser Leu Gly Cys Leu . . 20 . 30 25 Leu Tyr Glu Met Ala Ala Leu Gln Ser Pro Phe Tyr Gly Asp Lys Met 35 40 45 Asn Leu Tyr Ser Leu Cys Lys Lys Ile Glu Gln Cys Asp Tyr Pro Pro 55 60 Leu Pro Ser Asp His Tyr Ser Glu Glu Leu Arg Gln Leu Val Asn Ile 70 75 Cys Ile Asn Pro Asp Pro Glu Lys Arg Pro Asp Ile Ala Tyr Val Tyr 85 90 Asp Val Ala Lys Arg Met His Ala Cys Thr Ala Ser Thr

<210> 334

<211> 787

<212> PRT

<213> Mouse

<400> 334

Lys Val Glu Gly Glu Gly Arg Gly Arg Trp Ala Leu Gly Leu Leu Arg 10 Thr Phe Asp Ala Gly Glu Phe Ala Gly Trp Glu Lys Val Gly Ser Gly 20 25 Gly Phe Gly Gln Val Tyr Lys Val Arg His Val His Trp Lys Thr Trp 35 40 Leu Ala Ile Lys Cys Ser Pro Ser Leu His Val Asp Asp Arg Glu Arg 55 60 Met Glu Leu Leu Glu Glu Ala Lys Lys Met Glu Met Ala Lys Phe Arg 70 75 Tyr Ile Leu Pro Val Tyr Gly Ile Cys Gln Glu Pro Val Gly Leu Val 90 85 95 Met Glu Tyr Met Glu Thr Gly Ser Leu Glu Lys Leu Leu Ala Ser Glu. 105 100 110 Pro Leu Pro Trp Asp Leu Arg Phe Arg Ile Val His Glu Thr Ala Val 120 , 125



| | 130 | Asn | | | | 135 | | | | | 140 | | | | |
|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|-------------------|
| Leu 145 | Lys | Pro | Ala | Asn | 11e 150 | Leu | Leu | Asp | Ala | His 155 | Tyr | His | Val | Lys | Ile 160 |
| | Asp | Phe | Gly | Leu 165 | Ala | Lys | Сув | Asn | Gly 170 | Met | Ser | His | Ser | His 175 | Asp |
| Leu | Ser | Met | Asp 180 | | Leu | Phe | Gly | Thr 185 | Ile | Ala | Tyr | Leu | Pro 190 | Pro | Glu |
| Arg | Ile | Arg 195 | | Lys | Ser | Arg | Leu 200 | Phe | Asp | Thr | Lys | His 205 | Asp | Val | Tyr |
| Ser | Phe 210 | Ala | Ile | Val | Ile | Trp 215 | Gly | Val | Leu | Thr | Gln 220 | Lys | Lys | Pro | Phe |
| Ala 225 | | Glu | Lys | Asn | Ile 230 | Leu | His | Ile | Met | Met 235 | Lys | Val | Val | Lys | Gly 240 |
| | Arg | Pro | Glu | Leu 245 | Pro | Pro | Ile | Cys | Arg 250 | Pro | Arg | Pro | Arg | Ala 255 | Суз |
| Ala | Ser | Leu | Ile 260 | Gly | Leu | Met | Gln | Arg 265 | Cys | Trp | His | Ala | Asp 270 | Pro | Gln |
| Val | Arg | Pro 275 | Thr | Phe | Gln | Glu | Ile 280 | Thr | Ser | Glu | Thr | Glu 285 | Asp | Leu | Cys |
| Glu | Lys 290 | Pro | Asp | Glu | Glu | Val 295 | Lys | Asp | Leu | Ala | His 300 | Glu | Pro | Gly | Glu |
| Lys 305 | Ser | Ser | Leu | Glu | Ser 310 | Lys | Ser | Glu | Ala | Arg 315 | Pro | Glu | Ser | Ser | Arg 320 |
| | - | Arg | | 325 | | | | | 330 | | | | | 335 | |
| | | Leu | 340 | | | | | 345 | | | | | 350 | | |
| | | Glu 355 | | | | | 360 | | | | | 365 | | | |
| | 370 | Gly | | | | 375 | | | | | 380 | | | | |
| 385 | | Ārg | • | | 390 | | | | | 395 | | | | | 400 |
| | | Leu | | 405 | | | | | 410 | | | | | 415 | |
| | | Ser | 420 | | | | | 425 | | | | | 430 | | |
| _ | | Asp 435 | | | | | 440 | | | | | 445 | | | |
| | 450 | Ala | _ | | | 455 | | | | | 460 | | | | |
| 465 | | Pro | | | 470 | | | | | 475 | | | | | 480 |
| | | Glu | | 485 | | | | | 490 | | | | | 495 | |
| | | Ser | 500 | | | | | 505 | | | | | 510 | | |
| | | 515 | | | | | 520 | | | | | 525 | | | Glu |
| _ | 530 | | | | | 535 | | | | | 540 | | | | Met |
| 545 | | | | | 550 | | | | | 555 | | | | | Leu 560 Pro |
| | | | | 565 | | | | | 570 | | | | | 575 | Leu |
| שפע | UTR | TAL | wrg | nia | ıτρ | GTU | отд | 1172 | neu | | -10 | * 01 | د لات | 200 | |



```
585
Ala Lys Gln Pro Gly Val Ser Val Asn Ala Gln Thr Leu Asp Gly Arg
     595
                        600
                                          605
Thr Pro Leu His Leu Ala Ala Gln Arg Gly His Tyr Arg Val Ala Arg
                    615
  610
                                       620
Ile Leu Ile Asp Leu Cys Ser Asp Val Asn Ile Cys Ser Leu Gln Ala 625 630 635 640
               630
Gln Thr Pro Leu His Val Alà Ala Glu Thr Gly His Thr Ser Thr Ala
                                650
Arg Leu Leu His Arg Gly Ala Gly Lys Glu Ala Leu Thr Ser Glu
          660
                            665
                                               670
Gly Tyr Thr Ala Leu His Leu Ala Ala Gln Asn Gly His Leu Ala Thr
      675
                        680
                                            685
Val Lys Leu Leu Ile Glu Glu Lys Ala Asp Val Met Ala Arg Gly Pro
            695
   690
                                     700
Leu Asn Gln Thr Ala Leu His Leu Ala Ala Ala Arg Gly His Ser Glu
         710
                                   715
Val Val Glu Glu Leu Val Ser Ala Asp Leu Ile Asp Leu Ser Asp Glu
725 730 735
                       730
Gln Gly Leu Ser Ala Leu His Leu Ala Ala Gln Gly Arg His Ser Gln 740 745 750
Thr Val Glu Thr Leu Leu Lys His Gly Ala His Ile Asn Leu Gln Ser
    755 760 765
Leu Lys Phe Gln Gly Gly Gln Ser Ser Ala Ala Thr Leu Leu Arg Arg
                      775
 770
Ser Lys Thr
785
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Ser Phe Val Glu Glu Val Glu Arg His Leu Glu Cys Gly Cys Arg Ala

Cys Ser <210> 336 <211> 274 <212> PRT <213> Human <400> 336 Tyr Arg Tyr Cys Gln His Arg Cys Val Asn Leu Pro Gly Ser Phe Arg 1 5 10 15 Cys Gln Cys Glu Pro Gly Phe Gln Leu Gly Pro Asn Asn Arg Ser Cys
20 25 30 Val Asp Val Asn Glu Cys Asp Met Gly Ala Pro Cys Glu Gln Arg Cys 35 40 45 Phe Asn Ser Tyr Gly Thr Phe Leu Cys Arg Cys His Gln Gly Tyr Glu . 55 60 Leu His Arg Asp Gly Phe Ser Cys Ser Asp Ile Asp Glu Cys Ser Tyr 70 75 Ser Ser Tyr Leu Cys Gln Tyr Arg Cys Val Asn Glu Pro Gly Arg Phe 85 90 95 85 90 95 Ser Cys His Cys Pro Gln Gly Tyr Gln Leu Leu Ala Thr Arg Leu Cys 100 105 110

185

190

125

140

165 170 Arg Tyr Met Thr Ile Thr Ser Glu Arg Ser Val Pro Ala Asp Val Phe 180 185 190 Gln Ile Gln Ala Thr Ser Val Tyr Pro Gly Ala Tyr Asn Ala Phe Gln . 195 200 205 Ile Arg Ala Gly Asn Ser Gln Gly Asp Phe Tyr Ile Arg Gln Ile Asn 210 215 220 Asn Val Ser Ala Met Leu Val Leu Ala Arg Pro Val Thr Gly Pro Arg 230 235 Glu Tyr Val Leu Asp Leu Glu Met Val Thr Met Asn Ser Leu Met Ser 245 250

Tyr Arg Ala Ser Ser Val Leu Arg Leu Thr Val Phe Val Gly Ala Tyr 265

Gln Asp Ile Asp Glu Cys Glu Ser Gly Ala His Gln Cys Ser Glu Ala

Gln Thr Cys Val Asn Phe His Gly Gly Tyr Arg Cys Val Asp Thr Asn 130 135 140

Arg Cys Val Glu Pro Tyr Ile Gln Val Ser Glu Asn Arg Cys Leu Cys 145 150 155 160 Pro Ala Ser Asn Pro Leu Cys Arg Glu Gln Pro Ser Ser Ile Val His

120

Thr Phe

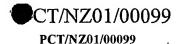
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180

115

135

<400> 337 · His Glu Glu Glu Pro Cys Asn Asn Gly Ser Glu Ile Leu Ala Tyr Asn 5 10 15 Ile Asp Leu Gly Asp Ser Cys Ile Thr Val Gly Asn Thr Thr His 25,



Val Met Lys Asn Leu Leu Pro Glu Thr Thr Tyr Arg Ile Arg Ile Gln 40 Ala Ile Asn Glu Ile Gly Val Gly Pro Phe Ser Gln Phe Ile Lys Ala 50 55 Lys Thr Arg Pro Leu Pro Pro Ser Pro Pro Arg Leu Glu Cys Ala Ala 70 75 Ser Gly Pro Gln Ser Leu Lys Leu Lys Trp Gly Asp Ser Asn Ser Lys 90 85 Thr His Ala Ala Gly Asp Met Val Tyr Thr Leu Gln Leu Glu Asp Arg 100 105 Asn Lys Arg Phe Ile Ser Ile Tyr Arg Gly Pro Ser His Thr Tyr Lys 120 115 125 Val Gln Arg Leu Thr Glu Phe Thr Cys Tyr Ser Phe Arg Ile Gln Ala . 135 130 140 Met Ser Glu Ala Gly Glu Gly Pro Tyr Ser Glu Thr Tyr Thr Phe Ser 150 155 Thr Thr Lys Ser Val Pro Pro Thr Leu Lys Ala Pro Arg Val Thr Gln 165 170 . 175 Leu Glu Gly Asn Ser Cys Glu Ile Phe Trp Glu Thr Val Pro Pro Met 185 180 190 Arg Gly Asp Pro Val Ser Tyr Val Leu Gln Val Leu Val Gly Arg Asp 200 195 205 Ser Glu Tyr Lys Gln Val Tyr Lys Gly Glu Glu Ala Thr Phe Gln Ile 210 215 220 Ser Gly Leu Gln Ser Asn Thr Asp Tyr Arg Phe Arg Val Cys Ala Cys . 230 235 Arg Arg Cys Val Asp Thr Ser Gln Glu Leu Ser Gly Ala Phe Ser Pro 245 250 Ser Ala Ala Phe Met Leu Gln Gln Arg Glu Val Met Leu Thr Gly Asp 265 260 Leu Gly Gly Met Glu Glu Ala Lys Met Lys Gly Met Met Pro Thr Asp 280 Glu Gln Phe Ala Ala Leu Ile Val Leu Gly Phe Ala Thr Leu Ser Ile 290 295 300 Leu Phe Ala Phe Ile Leu Gln Tyr Phe Leu Met Lys 305 310

<210> 338 <211> 237

<212> PRT

<213> Mouse

<400> 338

Met Leu Ser Leu Arg Ser Leu Leu Pro His Leu Gly Leu Phe Leu Cys 1 5 10 Leu Ala Leu His Leu Ser Pro Ser Leu Ser Ala Ser Asp Asn Gly Ser 20 25 - 30 Cys Val Val Leu Asp Asn Ile Tyr Thr Ser Asp Ile Leu Glu Ile Ser . 40 35 Thr Met Ala Asn Val Ser Gly Gly Asp Val Thr Tyr Thr Val Thr Val 50 55 60 Pro Val Asn Asp Ser Val Ser Ala Val Ile Leu Lys Ala Val Lys Glu 70 75 · Asp Asp Ser Pro Val Gly Thr Trp Ser Gly Thr Tyr Glu Lys Cys Asn 85 95 90 Asp Ser Ser Val Tyr Tyr Asn Leu Thr Ser Gln Ser Gln Ser Val Phe 105 110



Gln Thr Asn Trp Thr Val Pro Thr Ser Glu Asp Val Thr Lys Val Asn 120 115 125 Leu Gln Val Leu Ile Val Val Asn Arg Thr Ala Ser Lys Ser Ser Val 135 130 140 Lys Met Glu Gln Val Gln Pro Ser Ala Ser Thr Pro Ile Pro Glu Ser 150 155 145 Ser Glu Thr Ser Gln Thr Ile Asn Thr Thr Pro Thr Val Asn Thr Ala 165 ` 170 Lys Thr Thr Ala Lys Asp Thr Ala Asn Thr Thr Ala Val Thr Thr Ala 180 185 190 Asn Thr Thr Ala Asn Thr Thr Ala Val Thr Thr Ala Lys Thr Thr Ala 200 205 Lys Ser Leu Ala Ile Arg Thr Leu Gly Ser Pro Leu Ala Gly Ala Leu 210 · 215 His Ile Leu Leu Val Phe Leu Ile Ser Lys Leu Leu Phe 230

<210> 339 <211> 469 <212> PRT <213> Mouse

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Ser Asp Gln Glu Thr Leu Arg Ile His Glu Arg Leu Val Ala Gly Ser 275 280 285 Leu Ala Gly Ala Ile Ala Gln Ser Ser Ile Tyr Pro Met Glu Val Leu 290 295 300 Lys Thr Arg Met Ala Leu Arg Lys Thr Gly Gln Tyr Ser Gly Met Leu 310 315 Asp Cys Ala Arg Arg Ile Leu Ala Lys Glu Gly Val Ala Ala Phe Tyr 325 Lys Gly Tyr Ile Pro Asn Met Leu Gly Ile Ile Pro Tyr Ala Gly Ile 340 345 Asp Leu Ala Val Tyr Glu Thr Leu Lys Asn Thr Trp Leu Gln Arg Tyr 360 355 365 Ala Val Asn Ser Ala Asp Pro Gly Val Phe Val Leu Leu Ala Cys Gly 370 375 380 Thr Ile Ser Ser Thr Cys Gly Gln Leu Ala Ser Tyr Pro Leu Ala Leu 385 390 395 Val Arg Thr Arg Met Gln Ala Gln Ala Ser Ile Glu Gly Ala Pro Glu 405 410 415 Val Thr Met Ser Ser Leu Phe Lys Gln Ile Leu Arg Thr Glu Gly Ala 425 420 430 Phe Gly Leu Tyr Arg Gly Leu Ala Pro Asn Phe Met Lys Val Ile Pro 440 435 445 Ala Val Ser Ile Ser Tyr Val Val Tyr Glu Asn Leu Lys Ile Thr Leu 450 455 460 Gly Val Gln Ser Arg 465

<210> 340 <211> 99 <212> PRT <213> Mouse

<400> 340 Met Arg Leu Leu Ala Ala Leu Leu Leu Leu Leu Leu Ala Leu Cys 10 Ala Ser Arg Val Asp Gly Ser Lys Cys Lys Cys Ser Arg Lys Gly Pro 25 20 Lys Ile Arg Tyr Ser Asp Val Lys Lys Leu Glu Met Lys Pro Lys Tyr 40 Pro His Cys Glu Glu Lys Met Val Ile Val Thr Thr Lys Ser Met Ser 55 60 50 Arg Tyr Arg Gly Gln Glu His Cys Leu His Pro Lys Leu Gln Ser Thr 70 75 80 Lys Arg Phe Ile Lys Trp Tyr Asn Ala Trp Asn Glu Lys Arg Arg Val 85 90 95 Tyr Glu Glu

<210> 341 <211> 431 <212> PRT <213> Mouse

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Gln Leu Trp Leu Phe Arg Phe Leu Leu Asn Val Ala Gly Tyr Ala Ser
                           40
Phe Met Val Pro Gly Tyr Leu Leu Val Gln Tyr Leu Arg Arg Lys Asn
                      55
Tyr Leu Glu Thr Gly Arg Gly Leu Cys Phe Pro Leu Val Lys Ala Cys 65 70 75 80
Val Phe Gly Asn Glu Pro Lys Ala Pro Asp Glu Val Leu Leu Ala Pro
              85
                              90
Arg Thr Glu Thr Ala Glu Ser Thr Pro Ser Trp Gln Val Leu Lys Leu
          100
                            105
                                                 110
Val Phe Cys Ala Ser Gly Leu Gln Val Ser Tyr Leu Thr Trp Gly Ile
115 120 125
       115
                         120
                                             125
Leu Gln Glu Arg Val Met Thr Gly Ser Tyr Gly Ala Thr Ala Thr Ser
             135
                                140
Pro Gly Glu His Phe Thr Asp Ser Gln Phe Leu Val Leu Met Asn Arg
                 150
                                    155
Val Leu Ala Leu Val Val Ala Gly Leu Tyr Cys Val Leu Arg Lys Gln
                               170
              165
Pro Arg His Gly Ala Pro Met Tyr Arg Tyr Ser Phe Ala Ser Leu Ser
          180
                              185
                                               190
Asn Val Leu Ser Ser Trp Cys Gln Tyr Glu Ala Leu Lys Phe Val Ser
                          200
Phe Pro Thr Gln Val Leu Ala Lys Ala Ser Lys Val Ile Pro Val Met
                      215
                                         220
Met Met Gly Lys Leu Val Ser Arg Arg Ser Tyr Glu His Trp Glu Tyr
                230
                                   235
Leu Thr Ala Gly Leu Ile Ser Ile Gly Val Ser Met Phe Leu Leu Ser 245 250 255
Ser Gly Pro Glu Pro Arg Ser Ser Pro Ala Thr Thr Leu Ser Gly Leu
          260
                             265
                                                 270
Val Leu Leu Ala Gly Tyr Ile Ala Phe Asp Ser Phe Thr Ser Asn Trp
                        280
                                           285
      275
Gln Asp Ala Leu Phe Ala Tyr Lys Met Ser Ser Val Gln Met Met Phe 290 295 300
Gly Val Asn Leu Phe Ser Cys Leu Phe Thr Val Gly Ser Leu Leu Glu
         310
                                    315
Gln Gly Ala Leu Leu Glu Gly Ala Arg Phe Met Gly Arg His Ser Glu
               325
                                  330
                                                     335
Phe Ala Leu His Ala Leu Leu Leu Ser Ile Cys Ser Ala Phe Gly Gln
          340
                             345
                                                 350
Leu Phe Ile Phe Tyr Thr Ile Gly Gln Phe Gly Ala Ala Val Phe Thr 355 360 365
Ile Ile Met Thr Leu Arg Gln Ala Ile Ala Ile Leu Leu Ser Cys Leu
                      375
                                         380
Leu Tyr Gly His Thr Val Thr Val Val Gly Gly Leu Gly Val Ala Val
                390
                                     395
Val Phe Thr Ala Leu Leu Leu Arg Val Tyr Ala Arg Gly Arg Lys Gln
405 410 415
             405
                                 410
                                                  415
Arg Gly Lys Lys Ala Val Pro Thr Glu Pro Pro Val Gln Lys Val
                              425
           420
                                                  430
     <210> 342
     <211> 51
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<212> PRT

<213> Mouse

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<400> 342
Leu Lys Phe Ser His Pro Cys Leu Glu Asp His Asn Ser Tyr Cys Ile
Asn Gly Ala Cys Ala Phe His His Glu Leu Lys Gln Ala Ile Cys Arg
          20
                              25
Cys Phe Thr Gly Tyr Thr Gly Gln Arg Cys Glu His Leu Thr Leu Thr
                       . 40
      35
                                               45
Ser Tyr Ala
   50
     <210> 343
     <211> 51
     <212> PRT
     <213> Human
     <400> 343
Leu Lys Phe Ser His Leu Cys Leu Glu Asp His Asn Ser Tyr Cys Ile
                                   1:0
Asn Gly Ala Cys Ala Phe His His Glu Leu Glu Lys Ala Ile Cys Arg
                               25
Cys Phe Thr Gly Tyr Thr Gly Glu Arg Cys Glu His Leu Thr Leu Thr
     35
                           40
Ser Tyr Ala
   50
      <210> 344
     <211> 95
     <212> PRT
     <213> Human
     <400> 344
Ala Ala Ala Leu Leu Leu Leu Leu Leu Ala Leu Tyr Thr Ala Arg Val
                                   10
Asp Gly Ser Lys Cys Lys Cys Ser Arg Lys Gly Pro Lys Ile Arg Tyr
           20
                               25
                                                   30
Ser Asp Val Lys Lys Leu Glu Met Lys Pro Lys Tyr Pro His Cys Glu
     - 35
                                              45
                          40
Glu Lys Met Val Ile Ile Thr Thr Lys Ser Val Ser Arg Tyr Arg Gly
  50
                       55
                                          60
Gln Glu His Cys Leu His Pro Lys Leu Gln Ser Thr Lys Arg Phe Ile
                 70
                                     75
Lys Trp Tyr Asn Ala Trp Asn Glu Lys Arg Arg Val Tyr Glu Glu
            85
                                   90
      <210> 345
      <211> 77
      <212> PRT
      <213> Mouse
      <400> 345
Ser Lys Cys Lys Cys Ser Arg Lys Gly Pro Lys Ile Arg Tyr Ser Asp
                5
                                  10
Val Lys Lys Leu Glu Met Lys Pro Lys Tyr Pro His Cys Glu Glu Lys
          20
                              25
Met Val Ile Val Thr Thr Lys Ser Met Ser Arg Tyr Arg Gly Gln Glu
       35
                           40
                                              45
His Cys Leu His Pro Lys Leu Gln Ser Thr Lys Arg Phe Ile Lys Trp
    50
                       55
                                           60
```



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Tyr Asn Ala Trp Asn Glu Lys Arg Arg Val Tyr Glu Glu
                  70
     <210> 346
     <211> 77
     <212> PRT
     <213> Human
     <400> 346
Ser Lys Cys Lys Cys Ser Arg Lys Gly Pro Lys Ile Arg Tyr Ser Asp
                                10
Val Lys Lys Leu Glu Met Lys Pro Lys Tyr Pro His Cys Glu Glu Lys
         20
                          25
Met Val Ile Ile Thr Thr Lys Ser Val Ser Arg Tyr Arg Gly Gln Glu
              40
     35
                                          45
His Cys Leu His Pro Lys Leu Gln Ser Thr Lys Arg Phe Ile Lys Trp
                    55
                                      60
  50
Tyr Asn Ala Trp Asn Glu Lys Arg Arg Val Tyr Glu Glu
                 70
     <210> 347
     <211> 215
     <212> PRT
     <213> Mouse
     <400> 347
Met Leu Ser Leu Arg Ser Leu Leu Pro His Leu Gly Leu Phe Leu Cys 1 5 10 15
Leu Ala Leu His Leu Ser Pro Ser Leu Ser Ala Ser Asp Asn Gly Ser
                       25
                                     . 30
      20
Cys Val Val Leu Asp Asn Ile Tyr Thr Ser Asp Ile Leu Glu Ile Ser
    35
                        40
                                          45
Thr Met Ala Asn Val Ser Gly Gly Asp Val Thr Tyr Thr Val Thr Val
                   55
                                     60
Pro Val Asn Asp Ser Val Ser Ala Val Ile Leu Lys Ala Val Lys Glu
                70
                                  75
Asp Asp Ser Pro Val Gly Thr Trp Ser Gly Thr Tyr Glu Lys Cys Asn
             85
                             90
Asp Ser Ser Val Tyr Tyr Asn Leu Thr Ser Gln Ser Gln Ser Val Phe
                            105
          100
                                               110
Gln Thr Asn Trp Thr Val Pro Thr Ser Glu Asp Val Thr Lys Val Asn
                        120
                                           125
Leu Gln Val Leu Ile Val Val Asn Arg Thr Ala Ser Lys Ser Ser Val
   130
                      135 ·
                                        140
Lys Met Glu Gln Val Gln Pro Ser Ala Ser Thr Pro Ile Pro Glu Ser .
                 150
                                   155 '
Ser Glu Thr Ser Gln Thr Ile Asn Thr Thr Pro Thr Val Asn Thr Ala
             165
                                170
                                                  175
Lys Thr Thr Ala Lys Asp Thr Ala Asn Thr Thr Ala Val Thr Thr Ala
          180
                            185
                                              190
Asn Thr Thr Ala Asn Thr Thr Ala Val Thr Thr Ala Lys Thr Thr Ala
     195 200
                                            205
Lys Ser Leu Ala Ile Arg Thr
                     215
     <210> 348
     <211> 21
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      <213> Mouse
      <400> 348
Gly Tyr Ser Asp Gly Tyr Gln Val Cys Ser Arg Phe Gly Ser Lys Val
                                   10
Pro Gln Phe Leu Asn
      <210> 349
      <211> 417
      <212> DNA
      <213> Mouse
      <400> 349
getageegtg caeceagete teeggagege gtgeaggega geegagegee eegteegegg
                                                                        60
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| | atgtggatgà aaggtagcta | gtgtgagaca ccgctgtgtc | gtggtgtgtc tgtgctgaag | caggagagaa gcttcagaca | 480 |
| ggaggacggc atctgtgtga | atgtggatgà aaggtagcta aggagcagat | gtgtgagaca ccgctgtgtc cccagagtcg | gtggtgtgtc tgtgctgaag gcgggcttct | caggagagaa gcttcagaca tcgcggagat | 480 540 |
| ggaggacggc atctgtgtga gacagaggac gaaatggtgg | atgtggatgå aaggtagcta aggagcagat teetgeagca | gtgtgagaca ccgctgtgtc cccagagtcg gatgttcttt | gtggtgtgtc tgtgctgaag gcgggcttct ggtgtgatca | caggagagaa gcttcagaca tcgcggagat tctgtgcact | 480 540 600 |
| ggaggacggc atctgtgtga | atgtggatga aaggtagcta aggagcagat tcctgcagca gggacttggt | gtgtgagaca ccgctgtgtc cccagagtcg gatgttcttt gttcaccgcc | gtggtgtgtc tgtgctgaag gcgggcttct ggtgtgatca atcttcattg | caggagagaa gcttcagaca tcgcggagat tctgtgcact gagctgtggc | 480 540 |

| gggtagataa tecetgeeac ttatttetet etceegetgg | cacttacagg acacctggga | atttcctccc cagcattgtt | acccaggctg tctc | cccctagagg | 780 824 |
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| <213> Mouse | | | | | |
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| cgggcggcat cccccggccg | ccgcacgcac | aggccggcgc | cctccttgcc | tecetgetec | 180 |
| ccacegegee ceteeggeea | gcatgaggct | cctggcggcc | gcgctgctcc | tgctgctcct | 240 |
| ggcgctgtgc gcctcgcgcg | | | | | 300 |
| gatccgctac agcgacgtga | | | | | 360 |
| gaagatggtt atcgtcacca | | | | | 420 |
| gcaccctaag ctgcagagca | | | | | 480 |
| gcgcagggtc tacgaagaat | | | | | 540 |
| agagacttca gcagaggact | | | | | 600 |
| aagacaaatt atatattgct | | | | | 660 |
| gctgtgtgtg aaaggcttcc | agatgtgaga | rccagerege | ctgcgcacca | gacttcatta | 720 |
| caagtggctt tttgctgggc | tataastata | gggcgggggg | accteaagee | tttccttttt | 780 |
| aaaataaggg gttttgtatt | | | | | 840 |
| gggaggaaca gtgagcatgg | | | | | 900 960 |
| caaagcttcc gctcagagag tatgactggt cagagtttca | | | | | 1020 |
| gcaggtcctt ctacatctgt | accteaacce | actgaggete | cttaggagg | gcaactggga | 1020 |
| ccccaccca ccccacccg | caccccacct | catterereta | tracragga | ggageteeat | 1140 |
| cttaaaggag ctgggtcttt | ttcttgcaaa | ctgagggttt | ctgaaaggtg | gcaagcgatc | 1200 |
| gtagaagatg cttctgaggc | | | | | 1260 |
| ttcgggagga caagggaaga | | | | | 1320 |
| cctcttggca atgggagctc | cccccccca | aagctttgtt | tettteeete | accccaacag | 1380 |
| aaagtgcact cccctcagt | gaatacgcaa | acagcactgt | tctctgagtt | aggatgttag | 1440 |
| gacgatectg egecetgeee | teteetgtgt | acatattgcc | ttcagtaccc | ctccccacc | 1500 |
| ccatgccaca cactgcccct | cattagaggc | cgcactgtat | ggctgtgtat | ctgctatgta | 1560 |
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| <211> 568 | • | | | | , |
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| gttccaatat cagtctatct | | | | | 120 |
| gtgactgtaa cacctccaat | | _ | | | 180 |
| getgacaaca tagaaggace | | | | | 240 |
| aacagttact gcatcaacgg | | | | | 300 |
| aggtgtctaa aattgaaatc | | | | | 360 |
| ggcctttgtg aagaattttc | | | | | 420 |
| ttttcagatg aaacaacaaa | | | | | 480 |
| gatcacaatg aaatgagaag | | | | | 540 |
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<212> DNA <213> Rat

<400> 372

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| ggggctgctg | ctgtgccgca | ggagtggaga | gaccccgtga | gctgagccct | gcgccccgca | 180 |
| tcaccgctcg | gcgcccccaa | ggctgcctga | atacccggtg | cgccccggcg | cgcgacatga | 240 |
| | | gctttggacc | | | | 300 |
| gggaatccac | tttgatcagg | gccaccatta | ctgttaaagc | cccctcctca | gccttgtact | 360 |
| cttcccactg | gaatcggatt | tgctagaggg | tgccgtggaa | tcggaagtcc | tcccttgtcc | 420 |
| tcaagcaacc | agcctctgca | tettegegga | cactgcaagt | aggagctctt | ttaccaccaa | 480 |
| gttgaagtcg | cgctctgtcc | tcacagctgc | ttcggggtct | accccaagcc | tgagtcgggc | 540 |
| ctattgatat | tcaggacctg | aagttgccca | cggatcttgt | gctctgctag | aaaggcttgg | 600 |
| agagcggagg | aaagacgtgt | gcttctgtct | gctctcctgc | cccatatcac | tgttccatat | 660 |
| tactgtgtga | gcatctctcc | gggtgctgtg | ggctgcaaga | ccagcgccag | gaactgggcc | 720 |
| tcggacaccg | tccacttttc | acgcaaccga | aagctaaagt | ccctcaaagc | aaggggtctg | 780 |
| | | ggctggcaga | | | | 840 |
| cgatcttgaa | caaggtggcg | cctcatgcgt | gcccggccca | gtgctcctgt | tcaggcagca | 900 |
| cagtggactg | tcatgggctg | gcactgcgca | gtgtgcccag | gaatatcccc | cgcaacacgg | 960 |
| | | aataacatca | | | | 1020 |
| | | cagctcatgg | | | | 1080 |
| cattccagga | tcttaaggag | ctagaaagac | tgcgtttaaa | cagaaataac | cttcagttgt | 1140 |
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| | | aaggctttcc | | | | 1260 |
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| | | aacaatatta | | | | 1380 |
| | | cgactccact | | | | 1440 |
| cctggctctc | ggactggctt | cgccaaaggc | cacgggtggg | cttgtacact | cagtgtatgg | 1500 |
| gcccatccca | cctgaggggc | cataatgtag | cagaggttca | aaaacqaqaq | tttgtctgca | 1560 |
| | | gctccctcct | | | | 1620 |
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| | | caaggactgc | | | | 1860 |
| | | aaaagtttat | | | | 1920 |
| | | aactgccttc | | | | 1980 |
| | | gacaataagc | | | _ | 2040 |
| | | | | | gactgccatc | 2100 |
| | | ctccacacca | | | | 2160 |
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| - | | aacaaaatcc | | | | 2400 |
| | | | | | aagaaacttc | . 2460 |
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| | | aatgagattc | | | | 2580 |
| agcataagat | gttcaaagga | ttggagagcc | tcaaaacatt | gatgctgaga | agtaatcgaa | 2640 |
| | | agtttcacag | | | | 2700 |
| | | gttgcaccag | | | | 2760 |
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| aggaaatacc | aatccaggat | gtagccattc | aggacttcac | ctgtgatgac | ggaaacgatg | 2940 |
| ataatagctg | ctctccactc | tcccgttgtc | cttcggaatg | tacttgcttg | gatacagtag | 3000 |
| tacgatgtag | caacaagggc | ttgaaggtct | tacctaaagg | cattccaaga | gatgtcacag | 3060 |
| | | cagtttacac | | | | 3120 |
| | | agtaacaaca | | | | 3180 |
| | | | | | | |

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<210> 373
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<400> 373

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Ala Pro Ala Arg Ala Cys Gln Leu Pro Ser Glu Trp Arg Pro Leu Ser 20 25 30
Glu Gly Cys Arg Ala Glu Leu Ala Glu Trp Ile Val Tyr Ala Lys Val 35 40 45
Leu Ala Leu His Pro Glu Val Pro Gly Leu Tyr Asn Tyr Leu Pro Trp

<211> 83

<212> PRT <213> Mouse

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Arg Val Ser Pro Thr Ile Ser Leu Gln Glu Val His Val Asn Arg Glu
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                           25
Thr Met Gly Lys Ile Ala Val Ala Ser Lys Leu Met Trp Cys Ser Ala
  35
                       40
Ala Val Asp Ile Leu Phe Leu Leu Asp Gly Ser His Ser Ile Gly Lys 50 55 60
Gly Ser Phe Glu Arg Ser Lys Arg Phe Ala Ile Ala Ala Cys Asp Ala 65 70 75 80
Leu Asp Ile Ser Pro Gly Arg Val Arg Val Gly Ala Leu Gln Phe Gly
            85
                                                  95
                               90
Ser Thr Pro His Leu Glu Phe Pro Leu Asp Ser Phe Ser Thr Arg Gln
        100 105
                                        110
Glu Val Lys Glu Ser Ile Lys Gly Ile Val Phe Lys Gly Gly Arg Thr
115 120 125
Glu Thr Gly Leu Ala Leu Lys Arg Leu Ser Arg Gly Phe Pro Gly Gly
                    135 140
Arg Asn Gly Ser Val Pro Gln Ile Leu Ile Ile Val Thr Asp Gly Lys
          150
                                  155
Ser Gln Gly Pro Val Ala Leu Pro Ala Lys Gln Leu Arg Glu Arg Gly 165 170 175
Ile Val Val Phe Ala Val Gly Val Arg Phe Pro Arg Trp Asp Glu Leu 180 185 190
Leu Thr Leu Ala Ser Glu Pro Lys Asp Arg His Val Leu Leu Ala Glu
. 195
                      200
                                 205
Gln Val Glu Asp Ala Thr Asn Gly Leu Leu Ser Thr Leu Ser Ser Ser
            215
                             220
Ala Leu Cys Thr Thr Ala Asp Pro Asp Cys Arg Val Glu Pro His Pro 225 230 235 240
Cys Glu Arg Arg Thr Leu Glu Thr Val Arg Glu Leu Ala Gly Asn Ala
             245
                               250 255
Leu Cys Trp Arg Gly Ser Arg Gln Ala Asp Thr Val Leu Ala Leu Pro
         260
                   265
                                        270 .
Cys Pro Phe Tyr Ser Trp Lys Arg Val Phe Gln Thr His Pro Ala Asn 275 280 285
Cys Tyr Arg Thr Ile Cys Pro Gly Pro Cys Asp Ser Gln Pro Cys Gln 290 295 300
Asn Gly Gly Thr Cys Ile Pro Glu Gly Val Asp Arg Tyr His Cys Leu
                310
                                315
Cys Pro Leu Ala Phe Gly Gly Glu Val Asn Cys Ala Pro Lys Leu Ser
             325
                        330
                                                 335
Leu Glu Cys Arg Ile Asp Val Leu Phe Leu Leu Asp Ser Ser Ala Gly 340 345 350
                                           350
Thr Thr Leu Gly Gly Phe Arg Arg Ala Lys Ala Phe Val Lys Arg Phe
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355
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Val Gln Ala Val Leu Arg Glu Asp Ser Arg Ala Arg Val Gly Ile Ala
370 375
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Ser Tyr Gly Arg Asn Leu Met Val Ala Val Pro Cys Arg Gly Val Pro
385 390
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                                                    400
Ala Leu Cys Arg Thr
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Met Val Val Ala Gly Val Val Ala Leu Thr Leu Ala Leu Val Leu Ala
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                        25
                                            30
Trp Leu Ser Thr Tyr Val Ala Asp Ser Gly Asn Asn Gln Leu Leu Gly
                     40
                                        45
Thr Ile Val Ser Ala Gly Asp Thr Ser Val Leu His Leu Gly His Val 50 55 60
Asp Gln Leu Val Asn Gln Gly Thr Pro Glu Pro Thr Glu His Pro His
      · 70
                                 75
Pro Ser Gly Gly Asn Asp Asp Lys Ala Glu Glu Thr Ser Asp Ser Gly
             85
                     90
Gly Asp Ala Thr Gly Glu Pro Gly Ala Arg Gly Glu Met Glu Pro Ser
100 105 110
Leu Glu His Leu Leu Asp Ile Gln Gly Leu Pro Lys Arg Gln Ala Gly
 115 120
                               125
Leu Gly Ser Ser Arg Pro Glu Ala Pro Leu Gly Leu Asp Asp Gly Ser
130 135 140
Cys Leu Ser Pro Ser Pro Ser Leu Ile Asn Val Arg Leu Lys Phe Leu
145 150 155
                                                 160
Asn Asp Thr Glu Glu Leu Ala Val Ala Arg Pro Glu Asp Thr Val Gly
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Thr Leu Lys Arg
. 180
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     <211> 68
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His Leu Pro Leu Ile Pro Ser Val Gly Lys Ser Gln Cys Thr Gln Met 20 25 30
Trp His Cys Cys Met Pro Trp Val Cys Val Gly Asp Cys Leu Cys Leu 35 40 45
Ser Asp Pro Leu Trp Leu Cys Leu Leu Lys Glu Thr Glu Thr Pro Cys
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Gly Phe Leu Ser
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105

<210> 378 <211> 95 <212> PRT <213> Rat

100

<400> 378

 Met
 Trp
 Phe
 Leu
 Pro
 Cys
 Ser
 Val
 Pro
 Leu
 Val
 Ile
 Ser
 Ser
 Cys
 His

 1
 5
 10
 15
 15

 Ser
 Gln
 Ala
 Ser
 Pro
 His
 Trp
 Trp
 Trp
 Trp
 Gly
 Ile
 Ile
 Ser
 Arg
 Gly
 Gly
 Ala
 Trp
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 Ser
 Arg
 Gly
 Ile
 Ala
 Ile
 Ile

<210> 379 <211> 138 <212> PRT <213> Mouse

<400> 379

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Asn Leu His Leu Val Cys Val Asp Met Pro Gly His Glu Gly Thr Thr
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         100
                                              110.
Arg Ser Ser Leu Asp Asp Leu Ser Ile Val Gly Gln Val Lys Arg Ile
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His Gln Phe Val Glu Cys Leu Lys Leu Asn
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Met Ala Tyr Gly Ser Leu Val Phe Val Leu Leu Phe Ile Phe Val Lys
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                            25
                                             30
Arg Gln Ile Met Arg Phe Ala Met Lys Ser Arg Arg Gly Pro His Val
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Pro Val Gly His Asn Ala Pro Lys Asp Leu Lys Glu Glu Ile Asp Ile
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Arg Leu Ser Arg Val Gln Asp Ile Lys Tyr Glu Pro Gln Leu Leu Ala
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                                             30
Gly Gly Val Cys Trp Leu Gln Gln Gly Arg Glu Ala Thr Cys Ser Leu
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Val Leu Lys Thr Arg Val Ser Arg Glu Glu Cys Cys Ala Ser Gly Asn
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Ile Asn Thr Ala Trp Ser Asn Phe Thr His Pro Gly Asn Lys Ile Ser
                 70
                                 75
Leu Leu Gly Phe Leu Gly Leu Val His Cys Leu Pro Cys Lys Asp Ser
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Cys Asp Gly Val Glu Cys Gly Pro Gly Lys Ala Cys Arg Met Leu Gly
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                          105
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Gly Arg Pro Thr Leu Arg Ser Cys Val Pro Asn Cys Glu Gly Leu Pro
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               120
                                         125
Ala Gly Phe Gln Val Cys Gly Ser Asp Gly Ala Thr Tyr Arg Asp Glu
130 135 140
                   135
                                      140
Cys Glu Leu Arg Thr Ala Arg Cys Arg Gly His Pro Asp Leu Arg Val
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                                  155
Met Tyr Arg Gly Arg Cys Gln Lys Ser Cys Ala Gln Val Val Cys Pro
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Arg Pro Gln Ser Cys Leu Val Asp Gln Thr Gly Ser Ala His Cys Val
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                         185
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Val Cys Arg Ala Ala Pro Cys Pro Val Pro Ser Asn Pro Gly Gln Glu

200

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Gln Ala Thr Cys Phe Leu Gly Arg Ser Ile Gly Val Arg His Pro Gly
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Ile Cys Thr Gly Gly Pro Lys Val Pro Ala Glu Glu Glu Glu Asn Phe
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     <211> 285
     <212> PRT ·
     <213> Rat
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Pro Met Leu Gly Ala Phe Ala Arg Arg Asp Phe Gln Lys Gly Gly Pro
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Gln Leu Val Cys Ser Leu Pro Gly Pro Gln Gly Pro Pro Gly Pro Pro 35 40 45
Gly Ala Pro Gly Ser Ser Gly Met Val Gly Arg Met Gly Phe Pro Gly
        55
                                        60
Lys Asp Gly Gln Asp Gly Gln Asp Gly Asp Gly Asp Ser Gly Glu 65 70 75 80
                                  75
Glu Gly Pro Pro Gly Arg Thr Gly Asn Arg Gly Lys Gln Gly Pro Lys
85 90 95
              85
                             90
Gly Lys Ala Gly Ala Ile Gly Arg Ala Gly Pro Arg Gly Pro Lys Gly
                            105
                                      110
Val Ser Gly Thr Pro Gly Lys His Gly Ile Pro Gly Lys Lys Gly Pro
      115
                        120
                                            125
Lys Gly Lys Lys Gly Glu Pro Gly Leu Pro Gly Pro Cys Ser Cys Gly 130 135 140
Ser Ser Arg Ala Lys Ser Ala Phe Ser Val Ser Val Thr Lys Ser Tyr 145 150 155 160
Pro Arg Glu Arg Leu Pro Ile Lys Phe Asp Lys Ile Leu Met Asn Glu . 165 170 175
Gly Gly His Tyr Asn Ala Ser Ser Gly Lys Phe Val Cys Ser Val Pro
       180 185 190
Gly Ile Tyr Tyr Phe Thr Tyr Asp Ile Thr Leu Ala Asn Lys His Leu 195 200 205
Ala Ile Gly Leu Val His Asn Gly Gln Tyr Arg Ile Arg Thr Phe Asp
                    215
                                      220
Ala Asn Thr Gly Asn His Asp Val Ala Ser Gly Ser Thr Ile Leu Ala
               230
                                 235
Leu Lys Glu Gly Asp Glu Val. Trp Leu Gln Ile Phe Tyr Ser Glu Gln
             245
                       250 255
As Gly Leu Phe Tyr Asp Pro Tyr Trp Thr Asp Ser Leu Phe Thr Gly 260 265 270
        260
Phe Leu Ile Tyr Ala Asp Gln Gly Asp Pro Asn Glu Val
      275
                         280
                                        285
     <210> 383
     <211> 183
     <212> PRT
     <213> Rat
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PCT/NZ01/00099 WO 01/90357

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Met Lys Leu Cys Leu Val Ala Val Val Gly Cys Leu Leu Val Pro
                                 10
Pro Ala Gln Ala Asn Lys Ser Ser Glu Asp Ile Arg Cys Lys Cys Ile
       20
                             25
Cys Pro Pro Tyr Arg Asn Ile Ser Gly His Ile Tyr Asn Gln Asn Val
     35 ` 40
                                           45
Ser Gln Lys Asp Cys Asn Cys Leu His Val Val Glu Pro Met Pro Val
                    55
                                       60
Pro Gly His Asp Val Glu Ala Tyr Cys Leu Leu Cys Glu Cys Arg Tyr
       70
Glu Glu Arg Ser Thr Thr Thr Ile Lys Val Ile Ile Val Ile Tyr Leu
85 90 95
Ser Val Val Gly Ala Leu Leu Leu Tyr Met Ala Phe Leu Met Leu Val
         100 105
                                               110
Asp Pro Leu Ile Arg Lys Pro Asp Ala Tyr Thr Glu Gln Leu His Asn
                   120
      115
                                           125
Glu Glu Glu Asn Glu Asp Ala Arg Ser Met Ala Ala Ala Ala Ala Ser 130 135 140
Ile Gly Gly Pro Arg Ala Asn Thr Val Leu Glu Arg Val Glu Gly Ala
145 150 155
Gln Gln Arg Trp Lys Leu Gln Val Gln Glu Gln Arg Lys Thr Val Phe
165 170 175
                                170
Asp Arg His Lys Met Leu Ser
         180
     <210> 384
     <211> 292
     <212> PRT
     <213> Mouse
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Cys Gln Leu Pro Leu Arg Val Leu Ile Ile Ser Asn Asn Lys Leu Gly
1 5 10 15
Ala Leu Pro Pro Asp Ile Ser Thr Leu Gly Ser Leu Arg Gln Leu Asp
       20
                             25
Val Ser Ser Asn Glu Leu Gln Ser Leu Pro Val Glu Leu Cys Ser Leu
     35
                         40
Arg Ser Leu Arg Asp Leu Asn Val Arg Arg Asn Gln Leu Ser Thr Leu 50 55 60
                                     60
Pro Asp Glu Leu Gly Asp Leu Pro Leu Val Arg Leu Asp Phe Ser Cys 65 70 75 80
Asn Arg Ile Ser Arg Ile Pro Val Ser Phe Cys Arg Leu Arg His Leu
85 90 95
                                90
Gln Val Val Leu Leu Asp Ser Asn Pro Leu Gln Ser Pro Pro Ala Gln
                            105 ... 110
         100
Ile Cys Leu Lys Gly Lys Leu His Ile Phe Lys Tyr Leu Thr Met Glu
115 120 125
Ala Gly Arg Arg Gly Ala Ala Leu Gly Asp Leu Val Pro Ser Arg Pro
  130
                    135
                                  140
Pro Ser Phe Ser Pro Cys Pro Ala Glu Asp Leu Phe Pro Gly Arg Arg
               150
                                    155 .
Tyr Asp Gly Gly Leu Asp Ser Gly Phe His Ser Val Asp Ser Gly Ser
```

· 170

Lys Arg Trp Ser Gly Asn Glu Ser Thr Asp Asp Phe Ser Glu Leu Ser 185

175

190

```
Phe Arg Ile Ser Glu Leu Ala Arg Asp Pro Arg Gly Pro Arg Gln Pro
      195
                        200
Arg Glu Asp Gly Ala Gly Asp Gly Asp Leu Glu Gln Ile Asp Phe Ile
 210
                     215
                                       220
Asp Ser His Val Pro Gly Glu Asp Glu Asp Arg Ser Ala Ala Glu Glu 225 230 235
225
                 230
                                235
Gln Leu Pro Ser Glu Leu Ser Leu Val Ala Gly Asp Val Glu Lys Pro
245 250 255
Ser Ser Ser Arg Arg Glu Glu Pro Ala Gly Glu Glu Arg Arg Pro 260 265 270
Asp Thr Leu Gln Leu Trp Gln Glu Arg Glu Arg Lys Gln Gln Gln
               280
                                           285
Ser Gly Gly Trp
   290
     <210> 385
     <211> 164
     <212> PRT
     <213> Mouse
     <400> 385
Ser Arg Gln Leu Arg Ala Pro Arg Phe Asp Pro Arg Ala Gly Phe His
1 5
                    10
Ala Glu Gly Lys Asp Arg Gly Pro Ser Val Pro Gln Gly Leu Leu Lys
          20
                           25
                                              30
Ala Ala Arg Ser Ser Gly Gln Leu Asn Leu Ala Gly Arg Asn Leu Gly
     35
                       40
Glu Val Pro Gln Cys Val Trp Arg Ile Asn Val Asp Ile Pro Glu Glu 50 55 60
Ala Asn Gln Asn Leu Ser Phe Ser Ser Thr Glu Arg Trp Trp Asp Gln
65 70
                                  75
Thr Asp Leu Thr Lys Leu Ile Ile Ser Ser Asn Lys Leu Gln Ser Leu
            85
                           9.0
Ser Asp Asp Leu Arg Leu Leu Pro Ala Leu Thr Val Leu Asp Ile His
100 105 110
Asp Asn Gln Leu Thr Ser Leu Pro Ser Ala Ile Arg Glu Leu Asp Asn
 115 120 125
Leu Gln Lys Leu Asn Val Ser His Asn Lys Leu Lys Ile Leu Pro Glu
         · 135
                                     140
Glu Ile Thr Ser Leu Lys Asn Leu Arg Thr Leu His Leu Gln His Asn
                 150
                                 155
                                                     160
Glu Leu Thr Cys
     <210> 386
     <211> 71
     <212> PRT
     <213> Mouse
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Ser Leu Ser Ile Leu Pro Ala Val Arg Val Ser Pro Arg Pro Thr Tyr
                               10
Pro Ser Thr Ala Ser Ser Met Ala Ala Phe Leu Val Thr Gly Phe Phe
    . 20
                            25
Phe Ser Leu Phe Val Val Leu Gly Met Glu Pro Arg Ala Leu Phe Arg
     35
                     40
                                          45
Pro Asp Lys Ala Leu Pro Leu Ser Cys Ala Lys Pro Thr Ser Leu Cys
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50
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Val Gln Ser Ser Phe Leu Gly
                  70
     <210> 387
     <211> 126
     <212> PRT
     <213> Mouse
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Glu Tyr Glu Ala Arg Val Leu Glu Lys Ser Leu Arg Lys Glu Ser Arg
                                10
Asn Lys Glu Thr Asp Lys Val Lys Leu Thr Trp Arg Asp Arg Phe Pro
                           25
Ala Tyr Phe Thr Asn Leu Val Ser Ile Ile Phe Met Ile Ala Val Thr
       35
                       40
Phe Ala Ile Val Leu Gly Val Ile Ile Tyr Arg Ile Ser Thr Ala Ala
 50
                  55
                                     60
Ala Leu Ala Met Asn Ser Ser Pro Ser Val Arg Ser Asn Ile Arg Val
              70
                                 75
Thr Val Thr Ala Thr Ala Val Ile Ile Asn Leu Val Val Ile Ile Leu
85 90 95
Leu Asp Glu Val Tyr Gly Cys Ile Ala Arg Trp Leu Thr Lys Ile Gly
       100 105 110
Glu Cys His Val Gln Asp Ser Ile Gly Ser Met Gly Leu Gly
                      120
     <210> 388
     <211> 84
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Ala Ala Glu Asn Glu Met Pro Val Ala Val Gly Pro Tyr Gly Gln Ser
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Gln Pro Ser Cys Phe Asp Arg Val Lys Met Gly Phe Val Met Gly Cys
        20
                          25
Ala Val Gly Met Ala Ala Gly Ala Leu Phe Gly Thr Phe Ser Cys Leu
      35
            . 40
Arg Ile Gly Met Arg Gly Arg Glu Leu Met Gly Gly Ile Gly Lys Thr
                    55
                                       60
Met Met Gln Ser Gly Gly Thr Phe Gly Thr Phe Met Ala Ile Gly Met
                  70
Gly Ile Arg Cys
     <210> 389
     <211> 284
     <212> PRT
     <213> Rat
     <400> 389
Gly Gly Ser Ser Val Ser His Val Leu Arg Gly Ser Gly Gln Glu Arg
               5
                               10
Ser Pro Pro Pro Ala Ser Met Gln Pro Pro Trp Gly Leu Ala Leu Pro
                            25
Leu Leu Pro Trp Val Ala Gly Gly Val Gly Thr Ser Pro Arg Asp
```

```
Tyr Trp Leu Pro Ala Leu Ala His Gln Pro Gly Val Cys His Tyr Gly
                    55
  50
                                                60
Thr Lys Thr Ala Cys Cys Tyr Gly Trp Lys Arg Asn Ser Lys Gly Val 65 70 75 80
Cys Glu Ala Val Cys Glu Pro Arg Cys Lys Phe Gly Glu Cys Val Gly
85 90 95
Pro Asn Lys Cys Arg Cys Phè Pro Gly Tyr Thr Gly Lys. Thr Cys Ser 100 105 110
Gln Asp Val Asn Glu Cys Ala Phe Lys Pro Arg Pro Cys Gln His Arg
115 120 125
Cys Val Asn Thr His Gly Ser Tyr Lys Cys Phe Cys Leu Ser Gly His
130 135 140
Met Leu Leu Pro Asp Ala Thr Cys Ser Asn Ser Arg Thr Cys Ala Arg
145 150 155 160
Ile Asn Cys Gln Tyr Ser Cys Glu Asp Thr Ala Glu Gly Pro. Arg Cys
165 170 175
Val Cys Pro Ser Ser Gly Leu Arg Leu Gly Pro Asn Gly Arg Val Cys
180 185 190
Leu Asp Ile Asp Glu Cys Ala Ser Ser Lys Ala Val Cys Pro Ser Asn 195 200 205
Arg Arg Cys Val Asn Thr Phe Gly Ser Tyr Tyr Cys Lys Cys His Ile 210 \phantom{\bigg|}215\phantom{\bigg|}220\phantom{\bigg|}
Gly Phe Glu Leu Lys Tyr Ile Ser Arg Arg Tyr Asp Cys Val Asp Ile
225 230 235 240
Asn Glu Cys Thr Leu Asn Thr Arg Thr Cys Ser Pro His Ala Asn Cys
           245
                            250 255
Leu Asn Thr Gln Gly Ser Phe Lys Cys Lys Cys Lys Gln Gly Tyr Arg 260 265 270
Gly Asn Gly Leu Gln Cys Ser Val Ile Pro Glu His
       275
                               580.
      <210> 390
      <211> 85
      <212> PRT
      <213> Rat
      <400> 390
Gly Ala Pro Met Tyr Phe Ser Glu Gly Arg Glu Arg Gly Lys Val Tyr 1 10 15
                                       10
Val Tyr Asn Leu Arg Gln Asn Arg Phe Val Phe Asn Gly Thr Leu Lys 20 25 30
Asp Ser His Ser Tyr Gln Asn Ala Arg Phe Gly Ser Cys Ile Ala Ser . 35 40
Val Gln Asp Leu Asn Gln Asp Ser Tyr Asn Asp Val Val Gly Ala 50 55 60
Pro Gln Glu Asp Ser His Arg Gly Ala Ile Tyr Ile Phe His Gly Phe
Gln Thr Asn Ile Leu
                85
      <210> 391
      <211> 158
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       <213> Rat
       <400> 391
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Phe Gln Thr Asn Ile Leu Lys Lys Pro Val Gln Arg Ile Ser Ala Ser
               5
                                 10
Glu Leu Ala Pro Gly Leu Gln His Phe Gly Cys Ser Ile His Gly Gln
          20
                             25
                                                30
Leu Asp Leu Asn Glu Asp Gly Leu Val Asp Leu Ala Val Gly Ala Leu
      35
                         40
                                            45
Gly Asn Ala Val Val Leu Trp Ala Arg Pro Val Val Gln Ile Asn Ala
                   55`
                                       60
Ser Leu His Phe Glu Pro Ser Lys Ile Asn Ile Phe His Lys Asp Cys
                70
                                   75
Lys Arg Asn Gly Arg Asp Ala Thr Cys Leu Ala Ala Phe Leu Cys Phe
             85
                                90
Gly Pro Ile Phe Leu Ala Pro His Phe His Thr Ala Thr Val Gly Ile
          100
                             105
Arg Tyr Asn Ala Thr Met Asp Glu Arg Arg Tyr Met Pro Arg Ala His
                         120
                                       125
Leu Asp Glu Gly Ala Asp Gln Phe Thr Asn Arg Ala Val Leu Leu Ser
  130
                     135
                                        140
Ser Gly Gln Glu His Cys Gln Arg Ile Asn Phe His Val Leu
                  150
    <210> 392
     <211> 124
     <212> PRT
     <213> Mouse
     <400> 392
Ala Ala Glu Gln Glu Ala Ser Ser Arg Arg Arg Gly Gly Ala Gly
1
               5
                                 10
Pro Ala Leu Phe Ser Ser Gly Ser Leu Arg Ser Glu Pro Gln Pro Arg
    20
                             25
                                                30
Leu Pro Gln Ala Arg Ser Arg Pro Arg Pro Ser Phe Leu Gln Ala Arg
                         40
 35
Ser Arg Pro Cys Leu Ser Gln Ala Cys Ser Pro Ala Ala Ser Val Leu 50 60
        55
                                       60
Ser Ser Ser Ser Leu Cys Gly Arg Ser His Leu Leu Pro Gly Ser Leu
                 70
                                   75
Pro Ala Thr Ala Phe Leu Leu Leu Pro Gly Ser Leu Pro Gly Arg
              85
                                 90
                                                   95
Arg Pro Ser Ala Ala Gln Ala Ala Pro Val Leu Ala Trp Gly Leu Val
          100
                            105
Ala Phe Gln Leu Gly Val Ala Ala Gly Ala Gly Arg
       115
                          120
     <210> 393
     <211> 242
     <212> PRT
     <213> Rat
     <400> 393
Gly His Cys Asp Cys Gln Ala Gly Tyr Gly Gly Glu Ala Cys Gly Gln
                                 10
Cys Gly Leu Gly Tyr Phe Glu Ala Glu Arg Asn Ser Ser His Leu Val
                             25
         20
                                               30
Cys Ser Ala Cys Phe Gly Pro Cys Ala Arg Cys Thr Gly Pro Glu Glu
```

40

Ser His Cys Leu Gln Cys Arg Lys Gly Trp Ala Leu His His Leu Lys

35

```
50
                     55
                                      60 ·
Cys Val Asp Ile Asp Glu Cys Gly Thr Glu Gln Ala Thr Cys Gly Ala
                           75
          70
Asp Gln Phe Cys Val Asn Thr Glu Gly Ser Tyr Glu Cys Arg Asp Cys
        85
                              90
Ala Lys Ala Cys Leu Gly Cys Met Gly Ala Gly Pro Gly Pro Cys Lys
100 105 110
Lys Cys Ser Arg Gly Tyr Gln Gln Val Gly Ser Lys Cys Leu Asp Val
     115
                     120
                                    125
Asp Glu Cys Glu Thr Val Val Cys Pro Gly Glu Asn Glu Gln Cys Glu
130 135 140
Asn Thr Glu Gly Ser Tyr Arg Cys Val Cys Ala Glu Gly Phe Arg Gln 145 150 155 160
Glu Asp Gly Ile Cys Val Lys Glu Gln Ile Pro Glu Ser Ala Gly Phe
                   170 175
            165
Phe Ala Glu Met Thr Glu Asp Glu Met Val Val Leu Gln Gln Met Phe
                   185
                                             190
Phe Gly Val Ile Ile Cys Ala Leu Ala Thr Leu Ala Ala Lys Gly Asp
195 200 205
Leu Val Phe Thr Ala Ile Phe Ile Gly Ala Val Ala Ala Met Thr Gly
. 210
                 215 220
Tyr Trp Leu Ser Glu Arg Ser Asp Arg Val Leu Glu Gly Phe Ile Lys
225
              230
                                   235
Gly Arg
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<210> 394

<211> 99

<212> PRT

<213> Mouse

<400> 394

Met Arg Leu Leu Ala Ala Ala Leu Leu Leu Leu Leu Ala Leu Cys . 1 5 10 15 Ala Ser Arg Val Asp Gly Ser Lys Cys Lys Cys Ser Arg Lys Gly Pro 25 30 Lys Ile Arg Tyr Ser Asp Val Lys Lys Leu Glu Met Lys Pro Lys Tyr . 40 45 Pro His Cys Glu Glu Lys Met Val Ile Val Thr Thr Lys Ser Met Ser 50 55 60 Arg Tyr Arg Gly Gln Glu His Cys Leu His Pro Lys Leu Gln Ser Thr 70 75 Lys Arg Phe Ile Lys Trp Tyr Asn Ala Trp Asn Glu Lys Arg Arg Val 85 .. 90 Tyr Glu Glu

<210> 395

<211> 103

<212> PRT

<213> Human

<400> 395

Met Ala Leu Gly Val Pro Ile Ser Val Tyr Leu Leu Phe Asn Ala Met 1 5 10 15 Thr Ala Leu Thr Glu Glu Ala Ala Val Thr Val Thr Pro Pro Ile Thr 20 25 . 30

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Ala Gln Gln Gly Asn Trp Thr Val Asn Lys Thr Glu Ala Asp Asn Ile
       35
Glu Gly Pro Ile Ala Leu Lys Phe Ser His Leu Cys Leu Glu Asp His
                    55
                                       60
Asn Ser Tyr Cys Ile Asn Gly Ala Cys Ala Phe His His Glu Leu Glu
                 70
                                    75
Lys Ala Ile Cys Arg Cys Leu Lys Leu Lys Ser Pro Tyr Asn Val Cys
             85
                                90
Ser Gly Glu Arg Arg Pro Leu
          100
     <210> 396
     <211> 1529
     <212> PRT
     <213> Rat
     <400> 396
Met Ser Gly Ile Gly Trp Gln Thr Leu Ser Leu Ser Leu Ala Leu Val
1 5 10 15
Leu Ser Ile Leu Asn Lys Val Ala Pro His Ala Cys Pro Ala Gln Cys
 20
                            25
Ser Cys Ser Gly Ser Thr Val Asp Cys His Gly Leu Ala Leu Arg Ser
                      40
      35
                                            45
Val Pro Arg Asn Ile Pro Arg Asn Thr Glu Arg Leu Asp Leu Asn Gly
               55
                                       60
Asn Asn Ile Thr Arg Ile Thr Lys Thr Asp Phe Ala Gly Leu Arg His 65 70 75 80
                 70
                                 75
Leu Arg Val Leu Gln Leu Met Glu Asn Lys Ile Ser Thr Ile Glu Arg
85 90 95
Gly Ala Phe Gln Asp Leu Lys Glu Leu Glu Arg Leu Arg Leu Asn Arg
         100
                            105
                                               110
Asn Asn Leu Gln Leu Phe Pro Glu Leu Leu Phe Leu Gly Thr Ala Lys
               120 125
Leu Tyr Arg Leu Asp Leu Ser Glu Asn Gln Ile Gln Ala Ile Pro Arg
 130
           135
                                        140
Lys Ala Phe Arg Gly Ala Val Asp Ile Lys Asn Leu Gln Leu Asp Tyr
145 150
                                   155
Asn Gln Ile Ser Cys Ile Glu Asp Gly Ala Phe Arg Ala Leu Arg Asp
            165
                               170
                                           · 175
Leu Glu Val Leu Thr Leu Asn Asn Asn Asn Ile Thr Arg Leu Ser Val
Ala Ser Phe Asn His Met Pro Lys Leu Arg Thr Phe Arg Leu His Ser 195 200 205
                                        205
Asn Asn Leu Tyr Cys Asp Cys His Leu Ala Trp Leu Ser Asp Trp Leu
  210
                     215
                                        220
Arg Gln Arg Pro Arg Val Gly Leu Tyr Thr Gln Cys Met Gly Pro Ser 225 230 235 240
His Leu Arg Gly His Asn Val Ala Glu Val Gln Lys Arg Glu Phe Val
245 250 255
Cys Ser Gly His Gln Ser Phe Met Ala Pro Ser Cys Ser Val Leu His 260 ^{-\circ} 265 270
Cys Pro Ile Ala Cys Thr Cys Ser Asn Asn Ile Val Asp Cys Arg Gly
      275
                       280 . 285
Lys Gly Leu Thr Glu Ile Pro Thr Asn Leu Pro Glu Thr Ile Thr Glu
  290
                   295
                                      300
```

, 315

Ile Arg Leu Glu Gln Asn Ser Ile Arg Val Ile Pro Pro Gly Ala Phe

```
Ser Pro Tyr Lys Lys Leu Arg Arg Leu Asp Leu Ser Asn Asn Gln Ile
              325
                                330
Ser Glu Leu Ala Pro Asp Ala Phe Gln Gly Leu Arg Ser Leu Asn Ser
                   345
          340
                                            350
Leu Val Leu Tyr Gly Asn Lys Ile Thr Glu Leu Pro Lys Ser Leu Phe
      355
                        360
                                         365
Glu Gly Leu Phe Ser Leu Gln Leu Leu Leu Leu Asn Ala Asn Lys Ile
 370 375
                               380
Asn Cys Leu Arg Val Asp Ala Phe Gln Asp Leu His Asn Leu Asn Leu
     390
                                   395
Leu Ser Leu Tyr Asp Asn Lys Leu Gln Thr Val Ala Lys Gly Thr Phe
            405
                               410
Ser Ala Leu Arg Ala Ile Gln Thr Met His Leu Ala Gln Asn Pro Phe
                                      430
          420
                             425
Ile Cys Asp Cys His Leu Lys Trp Leu Ala Asp Tyr Leu His Thr Asn 435 ^\prime 440 445
Pro Ile Glu Thr Ser Gly Ala Arg Cys Thr Ser Pro Arg Arg Leu Ala
   450
                     455
                                       460
Asn Lys Arg Ile Gly Gln Ile Lys Ser Lys Lys Phe Arg Cys Ser Ala
          470
                                   475 .
Lys Glu Gln Tyr Phe Ile Pro Gly Thr Glu Asp Tyr Arg Ser Lys Leu 485 490 495
Ser Gly Asp Cys Phe Ala Asp Leu Ala Cys Pro Glu Lys Cys Arg Cys 500 510
Glu Gly Thr Thr Val Asp Cys Ser Asn Gln Lys Leu Asn Lys Ile Pro
     515
                        520
                                  525
Asp His Ile Pro Gln Tyr Thr Ala Glu Leu Arg Leu Asn Asn Asn Glu 530 540
Phe Thr Val Leu Glu Ala Thr Gly Ile Phe Lys Lys Leu Pro Gln Leu
545 550
                                  555
Arg Lys Ile Asn Leu Ser Asn Asn Lys Ile Thr Asp Ile Glu Glu Gly
             565
                               570
                                                  575
Ala Phe Glu Gly Ala Ser Gly Val Asn Glu Ile Leu Leu Thr Ser Asn
          580
                          585
                                      590
Arg Leu Glu Asn Val Gln His Lys Met Phe Lys Gly Leu Glu Ser Leu
     595
               600
Lys Thr Leu Met Leu Arg Ser Asn Arg Ile Ser Cys Val Gly Asn Asp
                     615
                               620
Ser Phe Thr Gly Leu Gly Ser Val Arg Leu Leu Ser Leu Tyr Asp Asn 625 630 635 640
Gln Ile Thr Thr Val Ala Pro Gly Ala Phe Gly Thr Leu His Ser Leu 645 650 655
Ser Thr Leu Asn Leu Leu Ala Asn Pro Phe Asn Cys Asn Cys His Leu
       660 665
Ala Trp Leu Gly Glu Trp Leu Arg Arg Lys Arg Ile Val Thr Gly Asn
      675
                       680
                                          685
Pro Arg Cys Gln Lys Pro Tyr Phe Leu Lys Glu Ile Pro Ile Gln Asp
                    695
                                      700
Val Ala Ile Gln Asp Phe Thr Cys Asp Asp Gly Asn Asp Asp Asp Ser
                  710
                                    715
Cys Ser Pro Leu Ser Arg Cys Pro Ser Glu Cys Thr Cys Leu Asp Thr
725 730 735
                       730
Val Val Arg Cys Ser Asn Lys Gly Leu Lys Val Leu Pro Lys Gly Ile 740 745 750
Pro Arg Asp Val Thr Glu Leu Tyr Leu Asp Gly Asn Gln Phe Thr Leu
755
                      760
Val Pro Lys Glu Leu Ser Asn Tyr Lys His Leu Thr Leu Ile Asp Leu
```

| 770 | | 775 | | | 780 | | | | |
|--|---|---|---|---|---|--|---|---|---|
| Ser Asn Asn 785 | | 790 | | | 795 | | | | 800 |
| Thr Gln Leu | Leu Thr 805 | | Leu S | Ser Tyr 810 | Asn Arg | Leu | Arg | Cys 815 | Ile |
| Pro Pro Arg | 820 | | 8 | 825 | | | 830 | | |
| His Gly Asn 835 | | | 840 | | | 845 | - | • | |
| Ser Ala Leu 850 | | 855 | | | 860 | , | | | _ |
| Cys Asn Met 865 | - | 870 | • - | _ | 875 | | - | - | 880 |
| Pro Gly Ile | 885 | | | 890 | | | - | 895 | |
| Leu Leu Thr | 900 | | 9 | 905 | | | 910 | | |
| Val Thr Ile 915 | | | 920 | | | 925 | | | |
| Asn Asp Gly 930 | | 935 | _ | | 940 | _ | _ | _ | |
| Cys Pro Tyr | | 950 | | | 955 | | | | 960 |
| Cys Ile Ser | 965 | • | | 970 | | • | | 975 | |
| Gly Glu Asn | 980 | | 9 | 985 | _ | _ | 990 | | _ |
| Glu Ser Cys 995 | | | 1000 | | | 1009 | 5 | | |
| Asn Asn Ser 1010 | | 101 | 5 | | 1020 |) | | | |
| Pro Pro Glu 1025 | | 1030 | | | 1035 | | | | 104 |
| Ala Gln Ásp | 104 | 5 | | 1050 |) | | | 1055 | i. |
| Pro Lys Gly | | | | | | T1 - | C111 | | His |
| | 1060 | | 1 | 1065 | | | 1070 | ì | |
| Cys Asp Ile | 1060 Asp Phe 5 | Asp Asp | 1 Cys G 1080 | 1065 Gln Asp | Asn Lys | Cys 1085 | 1070 Lys | Asn | Gly |
| Cys Asp Ile 107 Ala His Cys 1090 | 1060 Asp Phe 5 Thr Asp | Asp Asp Ala Val 109 | Cys G 1080 Asn G 5 | 1065 Gln Asp Gly Tyr | Asn Lys Thr Cys 1100 | Cys 1085 Val | 1070 Lys Cys | Asn Pro | Gly Glu |
| Cys Asp Ile 107 Ala His Cys 1090 Gly Tyr Ser 1105 | 1060 Asp Phe 5 Thr Asp Gly Leu | Asp Asp Ala Val 109 Phe Cys 1110 | Cys G 1080 Asn G 5 Glu F | 1065 Gln Asp Gly Tyr Phe Ser | Asn Lys Thr Cys 1100 Pro Pro 1115 | Cys 1085 Val) Met | 1070 Lys Cys Val | Asn Pro Leu | Gly Glu Leu 112 |
| Cys Asp Ile 107 Ala His Cys 1090 Gly Tyr Ser 1105 Arg Thr Ser | 1060 Asp Phe 5 Thr Asp Gly Leu Pro Cys 112 | Asp Asp Ala Val 109 Phe Cys 1110 Asp Asn 5 | Cys G 1080 Asn G 5 Glu F | 1065 Gln Asp Gly Tyr Phe Ser Asp Cys 1130 | Asn Lys Thr Cys 1100 Pro Pro 1115 Gln Asn | Cys 1085 Val) Met Gly | 1070 Lys Cys Val | Asn Pro Leu Gln 1135 | Gly Glu Leu 112 Cys |
| Cys Asp Ile 107 Ala His Cys 1090 Gly Tyr Ser 1105 Arg Thr Ser Ile Ile Arg | 1060 Asp Phe 5 Thr Asp Gly Leu Pro Cys 112 Val Asn 1140 | Asp Asp Ala Val 109 Phe Cys 1110 Asp Asn 5 Glu Pro | Cys G 1080 Asn G 5 Glu F Phe A Ile C | 1065 Gln Asp Gly Tyr Phe Ser Asp Cys 1130 Cys Gln 1145 | Asn Lys Thr Cys 1100 Pro Pro 1115 Gln Asn Cys Leu | Cys 1085 Val) Met Gly Pro | 1070 Lys Cys Val Ala Gly 1150 | Asn Pro Leu Gln 1135 Tyr | Gly Glu Leu 112 Cys Leu |
| Cys Asp Ile 107 Ala His Cys 1090 Gly Tyr Ser 1105 Arg Thr Ser Ile Ile Arg Gly Glu Lys 115 | 1060 Asp Phe 5 Thr Asp Gly Leu Pro Cys 112 Val Asn 1140 Cys Glu | Asp Asp Ala Val 109 Phe Cys 1110 Asp Asn 5 Glu Pro | Cys G 1080 Asn G 5 Glu F Phe A Ile C 1 Val S 1160 | Gly Tyr Phe Ser Asp Cys 1130 Cys Gln 1145 Ser Val | Asn Lys Thr Cys 1100 Pro Pro 1115 Gln Asn Cys Leu Asn Phe | Cys 1085 Val) Met Gly Pro Val 1165 | 1070 Lys Cys Val Ala Gly 1150 Asn | Asn Pro Leu Gln 1135 Tyr Lys | Gly Glu Leu 112 Cys Leu Glu |
| Cys Asp Ile 107 Ala His Cys 1090 Gly Tyr Ser 1105 Arg Thr Ser Ile Ile Arg Gly Glu Lys 2115 Ser Tyr Leu 1170 | 1060 Asp Phe 5 Thr Asp Gly Leu Pro Cys 112 Val Asn 1140 Cys Glu 5 Gln Ile | Asp Asp Ala Val 109 Phe Cys 1110 Asp Asn 5 Glu Pro Lys Leu Pro Ser 117 | 1 Cys G 1080 Asn G 5 Glu F Phe A Ile C 1 Val S 1160 Ala L | 1065 Gly Tyr Phe Ser Asp Cys 1130 Cys Gln 1145 Ser Val | Asn Lys Thr Cys 1100 Pro Pro 1115 Gln Asn Cys Leu Asn Phe Arg Pro 1180 | Cys 1085 Val) Met Gly Pro Val 1165 Gln | 1070 Lys Cys Val Ala Gly 1150 Asn | Asn Pro Leu Gln 1135 Tyr Lys Asn | Gly Glu Leu 112 Cys Leu Glu |
| Cys Asp Ile 107 Ala His Cys 1090 Gly Tyr Ser 1105 Arg Thr Ser Ile Ile Arg Gly Glu Lys 215 Ser Tyr Leu | 1060 Asp Phe 5 Thr Asp Gly Leu Pro Cys 112 Val Asn 1140 Cys Glu 5 Gln Ile | Asp Asp Ala Val 109 Phe Cys 1110 Asp Asn 5 Glu Pro Lys Leu Pro Ser 117 Thr Asp | 1 Cys G 1080 Asn G 5 Glu F Phe A Ile C 1 Val S 1160 Ala L | 1065 Gly Tyr Phe Ser Asp Cys 1130 Cys Gln 1145 Ser Val | Asn Lys Thr Cys 1100 Pro Pro 1115 Gln Asn Cys Leu Asn Phe Arg Pro 1180 Gly Ile | Cys 1085 Val) Met Gly Pro Val 1165 Gln | 1070 Lys Cys Val Ala Gly 1150 Asn | Asn Pro Leu Gln 1135 Tyr Lys Asn | Gly Glu Leu 112 Cys Leu Glu Glu Ile |
| Cys Asp Ile 107 Ala His Cys 1090 Gly Tyr Ser 1105 Arg Thr Ser Ile Ile Arg Gly Glu Lys 215 Ser Tyr Leu 1170 Thr Leu Gln | 1060 Asp Phe 5 Thr Asp Gly Leu Pro Cys 112 Val Asn 1140 Cys Glu 5 Gln Ile Ile Ala | Asp Asp Ala Val 109 Phe Cys 1110 Asp Asn 5 Glu Pro Lys Leu Pro Ser 117 Thr Asp 1190 Ile Ala | Cys G 1080 Asn G 5 Glu F Phe A Ile C 1160 Ala L 5 Glu A | 1065 Gly Tyr Phe Ser Asp Cys 1130 Cys Gln 1145 Ser Val Asp Ser | Asn Lys Thr Cys 1100 Pro Pro 1115 Gln Asn Cys Leu Asn Phe Arg Pro 1180 Gly Ile 1195 Tyr Arg | Cys 1085 Val) Met Gly Pro Val 1165 Gln) Leu | 1070 Lys Cys Val Ala Gly 1150 Asn Thr | Asn Pro Leu Gln 1135 Tyr Lys Asn | Gly Glu Leu 112 Cys Leu Glu Ile Lys 120 Arg |

```
Glu Thr Ile Asn Asp Gly Asn Phe His Ile Val Glu Leu Leu Thr Leu
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Met Glu Glu Phe Glu Gln Val Gln Ser Ile Ile Arg Ser Gln Thr Ser
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Met Gly Met Arg His Arg Asp Arg Pro Thr Thr Gly Asn Thr Leu Lys
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Ser Gly Leu Cys Ser Ala Leu Thr Thr Tyr Phe Phe Gly Ala Asp Leu 245 250 255
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Ala Arg Thr Val Ala Lys Val Glu Leu Ser Asp His Val Cys Asp Val 370 380
Val Phe Ala Leu Phe Asp Cys Asp Gly Asn Gly Glu Leu Ser Asn Lys
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Glu Phe Val Ser Ile Met Lys Gln Arg Leu Met Arg Gly Leu Glu Lys
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Pro Lys Asp Met Gly Phe Thr Arg Leu Met Gln Ala Met Trp Lys Cys
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PCT/NZ01/00099

Ser Leu Asn Ile Ala Ala Ser Ala Ala Val Gln Ala Ala Thr Lys Ser 135 130 140 Gln Gly Ala Leu Ala Gly Arg Leu Arg Ser Phe Ser Met Gln Asp Leu 150 145 155 Arg Ser Ile Pro Asp Thr Pro Val Pro Thr Tyr Gln Asp Pro Leu Tyr 170 165 175 Leu Glu Asp Gln Val Pro Arg Arg Pro Pro Ile Gly Tyr Arg Pro 185 180 190 Gly Gly Leu Gln Gly Ser Asp Thr Glu Asp Glu Cys Trp Ser Asp Asn 200 205 Glu Ile Val Pro Gln Pro Pro Val Gly Pro Arg Glu Lys Pro Leu Gly 215 220 Arg Ser Gln Ser Leu Arg Val Val Lys Arg Lys Pro Leu Thr Arg Glu 230 235 Gly Thr Ser Arg Ser Leu Lys Val Arg Thr Pro Lys Lys Ala Met Pro 245 250 Ser Asp Met Asp Ser 260

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<400> 462

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cacggagece tagectggtt ceaceaceag cgacgecgta teetgeagga gggtggegtg
                                                                      1680
gtaatcette tettetegee egeggeegtg gegeagtgte ageagtgget geageteeag
                                                                     1740
acagtggage cegggeegea tgaegeeete geegeetgge teagetgegt getaecegat
                                                                     1800
ttcctgcaag gccgggcgac cggccgctac gtcggggtct acttcgacgg gctgctgcac
                                                                     1860
ccagactetg tgccctcccc gttccgcgtc gccccgctct tctccctgcc ctcgcagctg
                                                                     1920
ceggetttee tggatgeact geagggagge tgeteeactt cegeggggeg accegeggae
                                                                     1980
cgggtggaac gagtgaccca ggcgctgcgg tccgccctgg acagctgtac ttctacctcg
                                                                     2040
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cccctacagt attcctaaaa aaaaaaaa
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Met Trp Phe Leu Pro Cys Ser Val Pro Leu Val Ile Ser Ser Cys His

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Glu Gly Leu Cys Arg Leu Trp Thr Ala Thr Cys His Ser Arg Gly Glu
                         40
Ser Glu Val Ser Arg Ser Ser Arg Lys Glu Asp Pro Arg Ile Pro Gln 50 55 60
Gly Ser Leu Ser Gly Asn Val Asp Phe Trp Arg Val Cys Pro Pro Cys
65 70
                           75 80
Ala His Thr Ser Met Asp Arg Thr Leu Gly Leu Leu Ser Cys Cys
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                                 90
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Leu Pro Met Ser Leu Ala Phe Leu Phe Phe Leu Phe Pro Ser Ala Ile
 20 25
                                     30
Leu Thr Leu Ile Val Cys His Ile Asn Ser Pro Gly Cys Val Phe Phe
    35 40
                                        4.5
Ser Arg Lys Lys Leu Lys Gly Lys Thr Lys Pro Lys Lys Pro Glu Thr
  50 55
Thr Asn Lys Asn Gly Asn Asp Asn Gly Cys Leu Ser Phe Phe Cys His 65 70 75 80
Asp Phe Pro Asp Leu Val Cys Ser Leu Cys Leu Arg Glu Ala Gly Asp 85 90 95
Val Asp Glu Ala Val Phe Phe Phe Leu Phe Leu Val Phe Glu Thr Arg
         100
                    105
                                      110
Val Ser Leu Cys His Pro Gly Trp Ser Val Thr Trp His Asp Leu Ser 115 120 125
Ser Leu Gln Pro Leu Pro Pro Gly Phe Lys Arg Leu Ser Cys Leu Ser
130 135 140
Leu Leu Ser Ser Trp Asp Tyr Arg His Ala Pro Leu Cys Pro Asp Asn
145 150 155 160
Phe Phe Val Phe Leu Val Glu Thr Gly Phe His His Val Gly Gln Ala
165 170 175
Gly Leu Glu Leu Leu Thr Ser Gly Tyr Pro Pro Thr Leu Ala Ser Gln 180 185 190
Ser Ala Gly Ile Ile Gly Met Asn His Arg Ala Trp Pro Lys Met
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                         200
                                            205
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Met Ser Gln Val Gln Val Ile Leu Leu Thr Leu Val Ser Gln Ser Val
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                                10 . 15
Gly Ile Ile Gly Met Ser His Cys Ile Lys Pro Val Lys Ser Ile Tyr
     20
                           25
                                           30
Ile Lys Leu Asp Cys Arg Lys Arg Arg Asp Lys Thr Ser Leu Leu Phe
```

Cys Pro Gln Gly Pro Arg Asn Pro Val Ser Lys Ala Pro His Gln Leu 50 55 60

Gln Cys Val Pro Val Ser Arg Val Pro Thr Gly Thr Glu Ser Ser Gly 65 70 75 80

Thr

<210> 491 <211> 193 <212> PRT <213> Human

<400> 491

Met Ala Pro Leu Leu Ser Leu Ser Cys Phe Trp Ala Asn Leu Leu Ala 1 5 10 Ile Arg Ser. Trp Leu Thr Arg Lys His Ile Gln Arg Leu His Ala Ala 20 25 Ala Thr Val Ile Lys Arg Ala Trp Gln Lys Trp Arg Ile Arg Met Ala Cys Leu Ala Ala Lys Glu Leu Asp Gly Val Glu Glu Lys His Phe Ser 50 55 60 Gln Ala Pro Cys Ser Leu Ser Thr Ser Pro Leu Gln Thr Arg Leu Leu 70 75 Glu Ala Ile Ile Arg Leu Trp Pro Leu Gly Leu Val Leu Ala Asn Thr 85 90 Ala Met Gly Val Gly Ser Phe Gln Arg Lys Leu Val Val Trp Ala Cys 100 105 110 Leu Gln Leu Pro Arg Gly Ser Pro Ser Ser Tyr Thr Val Gln Thr Ala 115 120 125 Gln Asp Gln Ala Gly Val Thr Ser Ile Arg Ala Leu Pro Gln Gly Ser 130 135 140 Ile Lys Phe His Cys Arg Lys Ser Pro Leu Arg Tyr Ala Asp Ile Cys 150 155 160 Pro Glu Pro Ser Pro Tyr Ser Ile Thr Gly Phe Asn Gln Ile Leu Leu 165 170 Glu Arg His Arg Leu Ile His Val Thr Ser Ser Ala Phe Thr Gly Leu 180 185 190

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PCT/NZ01/00099 **WO** 01/90357

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Leu Met Pro Ser Gly Gly Leu Thr
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Pro Thr Pro Gly Pro Asp Arg Asp Arg Glu Leu Thr Ala Asp Ser Asp
    35
              40
Val Asp Glu Phe Leu Asp Lys Phe Leu Ser Ala Gly Val Lys Gln Ser
 50 55
Asp Leu Pro Arg Lys Glu Thr Glu Gln Pro Pro Ala Pro Gly Ser Met 65
                               75
Glu Glu Ser Val Arg Gly Tyr Asp Trp Ser Pro Arg Asp Ala Arg Arg
            85
                              90
                                                95
Ser Pro Asp Gln Gly Arg Gln Gln Ala Glu Arg Arg Ser Val Leu Arg
     100 105 110
Gly Phe Cys Ala Asn Ser Ser Leu Ala Phe Pro Thr Lys Glu Arg Ala
    115
                    120
                            125
Phe Asp Asp Ile Pro Asn Ser Glu Leu Ser His Leu Ile Val Asp Asp
                             140
            135
Arg His Gly Ala Ile Tyr Cys Tyr Val Pro Lys Val Ala Cys Thr Asn 145 150 155 160
Trp Lys Arg Val Met Ile Val Leu Ser Gly Ser Leu Leu His Arg Gly
         165 170
                                               175
Ala Pro Tyr Arg Asp Pro Leu Arg Ile Pro Arg Glu His Val His Asn
         180 185
                                   . 190
Ala Ser Ala His Leu Thr Phe Asn Lys Phe Trp Arg Arg Tyr Gly Lys
195 200 205
Leu Ser Arg His Leu Met Lys Val Lys Leu Lys Lys Tyr Thr Lys Phe 210 215 220
Leu Phe Val Arg Asp Pro Phe Val Arg Leu Ile Ser Ala Phe Arg Ser
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Lys Phe Glu Leu Glu Asn Glu Glu Phe Tyr Arg Lys Phe Ala
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Val His Thr Pro Pro Leu Gly Pro Ile Leu Lys Lys Thr Ala Gly Leu
    35
                       40
Gly Phe Cys Ala Val Phe Leu Tyr Phe Ile Thr Ala Leu Ile Phe Pro
                    55
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Ala Ile Ser Thr Asn Ile Gln Pro Met His Lys Gly Thr Gly Ser Pro
               70
                                  75
Trp Thr Ser Lys Phe Tyr Val Pro Leu Thr Val Phe Leu Leu Phe Asn
            85
                              90 .
Phe Ala Asp Leu Cys Gly Arg Gln Val Thr Ala Trp Ile Gln Val Pro
        100 105
                                           110
Gly Pro Arg Ser Lys Leu Leu Pro Ile Leu Ala Val Ser Arg Val Cys
115 120 125
Leu Val Pro Leu Phe Leu Leu Cys Asn Tyr Gln Pro Arg Ser His Leu
  130 135 140
Thr Leu Val Leu Phe Gln Ser Asp Ile Tyr Pro Ile Leu Phe Thr Cys
145 . 150 . 155 . 160
Leu Leu Gly Leu Ser Asn Gly Tyr Leu Ser Thr Leu Val Leu Met Tyr
                     170 175
           165
Gly Pro Lys Ile Val Pro Arg Glu Leu Ala Glu Ala Thr Ser Val Val 180 185 190
Met Leu Phe Tyr Met Ser Leu Gly Leu Met Leu Gly Ser Ala Cys Ala
     195 200
Ala Leu Leu Glu His Phe Ile
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Leu Trp Ala Thr Ser Ser Phe Ala Ala Val Ser Pro Pro Ala Cys Ala
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Pro Ala Thr Ser Pro Ser Pro Val Val His Leu Arg Ser Thr Gln Pro
     35
                     40
                                        45
Gly Gln Ser Cys Phe Val Leu Leu His Arg Leu Gly Leu Pro Cys Val
            55
                                  60
Leu Ser Ser Ser Gly Ser Phe Ser Ser Pro His Leu Phe Cys Phe Leu
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65
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Pro Val Leu Val Ser Pro Cys Ala Leu Gly Pro
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Gly Leu His Leu Phe Leu Leu Thr Ala Gly Pro Ala Leu Gly Trp Asn
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Asp Pro Asp Arg Met Leu Leu Arg Asp Val Lys Ala Leu Thr Leu His
    35
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Tyr Asp Arg Tyr Thr Thr Ser Arg Arg Leu Asp Pro Ile Pro Gln Leu
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                             . 60
Lys Cys Val Gly Gly Thr Ala Gly Cys Asp Ser Tyr Thr Pro Lys Val
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Ile Gln Cys Gln Asn Lys Gly Trp Asp Gly Tyr Asp Val Gln Trp Glu

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Cys Lys Thr Asp Leu Asp Ile Ala Tyr Lys Phe Gly Lys Thr Val Val
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                      105
Ser Cys Glu Gly Tyr Glu Ser Ser Glu Asp Gln Tyr Val Leu Arg Gly
                120
     115
                                           125
Ser Cys Gly Leu Glu Tyr Asn Leu Asp Tyr Thr Glu Leu Gly Leu Gln
 130
                    135
                               140
Lys Leu Lys Glu Ser Gly Lys Gln His Gly Phe Ala Ser Phe Ser Asp
145 150 155
Tyr Tyr Tyr Lys Trp Ser Ser Ala Asp Ser Cys Asn Met Ser Gly Leu
             165
                                170
                                                175
Ile Thr Ile Val Val Leu Leu Gly Ile Ala Phe Val Val Tyr Lys Leu
                           185
                                     190
Phe Leu Ser Asp Gly Gln Tyr Ser Pro Pro Pro Tyr Ser Glu Tyr Pro
195 200 205
Pro Phe Ser His Arg Tyr Gln Arg Phe Thr Asn Ser Ala Gly Pro Pro
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     <210> 497
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Ala Arg Met Phe Pro Gly Asn Ala Gly Gly Glu Leu Val Thr Pro His
    20
                             25
Trp Val Leu Asp Gly Lys Thr Trp Leu Lys Val Thr Leu Lys Glu Gln
     35 40
Ile Ser Lys Pro Asp Ser Gly Leu Val Ala Leu Lys Ala Glu Gly Gln
          55<sup>i</sup>
                                       60
Asp Leu Leu Glu Leu Glu Lys Asn His Arg Leu Leu Ala Pro Gly 65 70 75 80
Tyr Thr Glu Thr Tyr Tyr Ser Arg Asp Gly Gln Pro Ile Val Leu Ser 85 90 95
Pro Asn His Thr Asp His Cys His Tyr Gln Gly Cys Val Arg Gly Phe
                                 . 110
                          105
Arg Glu Ser Trp Val Val Leu Ser Thr Cys Ser Gly Met Ser Gly Leu
                         120
                                           125
Ile Val Leu Ser Ser Lys Val Ser Tyr Tyr Leu His Pro Trp Met Pro
                     135
                                      140
Gly Asp Thr Lys Asp Phe Pro Thr His Lys Ile Phe Arg Val Glu Gln 145 150 150 165
Leu Phe Thr Trp Arg Gly Ala Arg Lys Asp Lys Asn Ser Gln Phe Lys
              165
                                170
Ala Gly Met Ala Arg Leu Pro His Val Pro His Arg Arg Met Arg Arg
                          185
        180
                                             190
Glu Ala Arg Arg Ser Pro Lys Tyr Leu Glu Leu Tyr Ile Val Ala Asp
195 200 205
His Ala Leu Phe Leu Leu Gln Arg Gln Asn Leu Asn His Thr Arg Gln
                    215 . 220
Arg Leu Leu Glu Ile Ala Asn Cys Val Asp Gln Ile Leu Arg Thr Leu
                230
                                   235
Asp Ile Gln Leu Val Leu Thr Gly Leu Glu Val Trp Thr Glu Gln Asp
              245
                               250
His Ser Arg Ile Thr Gln Asp Ala Asp Glu Thr Leu Trp Ala Phe Leu
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260
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Gln Trp Arg Arg Gly Leu Trp Val Arg Arg Pro His Asp Ser Thr Gln
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Leu Leu Thr Gly Arg Thr Phe Gln Gly Thr Thr Val Gly Leu Ala Pro
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                                          300
Val Glu Gly Met Cys His Ala Glu Ser Ser Gly Gly Val Ser Thr Asp 305 310 315 320
His Ser Glu Leu Pro Ile Gly Thr Ala Ala Thr Met Ala His Glu Ile
             325
                                330
Gly His Ser Leu Gly Leu His His Asp Pro Glu Gly Cys Cys Met Glu
           340
                              345
                                                  350
Ala Asp Ala Glu Gln Gly Gly Cys Val Met Glu Ala Ala Thr Gly His
                         360
                                    365
Pro Phe Pro Arg Val Phe Ser Ala Cys Ser Arg Arg Gln Leu Arg Thr
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                                         380
Phe Phe Arg Lys Gly Gly Gly Ala Cys Leu Ser Asn Val Ser Ala Pro
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                                     395
Gly Leu Leu Val Leu Pro Ser Arg Cys Gly Asn Gly Phe Val Glu Ala
405 415
                                 410
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Glu Glu Glu Cys Asp Cys Gly Ser Gly Gln Lys Arg Pro Asp Pro Cys
           420
                           425
Cys Phe Ala His Asn Cys Ser Leu Arg Ala Gly Ala Gln Cys Ala Gln
     435 440
Gly Asp Cys Cys Ala Arg Cys Leu Leu Lys Pro Ala Gly Thr Pro Cys
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                   455
                                         460
Arg Pro Ala Ala Asn Asp Cys Asp Leu Pro Glu Phe Cys Thr Gly Thr
465 470 475 480
Ser Pro His Cys Pro Ala Asp Val Tyr Leu Leu Asp Gly Ser Pro Cys
485 490 495
              485
                                                   495
Ala Glu Gly Arg Gly Tyr Cys Leu Asp Gly Trp Cys Pro Thr Leu Glu 500 505 . 510
Lys Gln Cys Gln Gln Leu Trp Gly Pro Gly Ser Gln Pro Ala Pro Glu
                          520
                                           525
Pro Cys Phe Gln Gln Met Asn Ser Val Gly Asn Ser Gln Gly Asn Cys
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                                       540
Gly Gln Asp Ser Lys Gly Ser Phe Leu Pro Cys Thr Gln Arg Asp Ala
545 550 555 560
Gln Cys Gly Lys Leu Leu Cys Gln Gly Gly Lys Pro Asn Pro Leu Val
              565
                                570
Pro His Val Val Thr Val Asp Ser Thr Ile Leu Leu Glu Gly Arg Gln
                          585
         580
                                                590
Val Leu Cys Arg Gly Ala Phe Val Leu Pro Asp Thr His Leu Asp Gln
595 600 605
       595
                        600
                                          605
Leu Gly Leu Gly Leu Val Glu Pro Gly Thr Arg Cys Gly Pro Arg Met
                     615
                                        620
Val Cys Gln Glu Arg His Cys Gln Asn Ala Thr Ser Gln Glu Leu Glu
                  630
                                     635 - 640
Arg Cys Ser Ser Gly Cys His Asn Arg Gly Val Cys Asn Ser Asn Arg
              645
                                 650
                                                    655
Asn Cys His Cys Ala Ala Gly Trp Ala Pro Pro Phe Cys Asp Lys Pro 660 665 670
Gly Leu Gly Gly Ser Val Asp Ser Gly Pro Ala Gln Ser Ala Asn Pro
      675
                          680
Asp Ala Phe Pro Leu Ala Met Leu Leu Ser Phe Leu Leu Pro Leu Leu
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                            700
Pro Gly Ala Gly Leu Ala Trp Cys Tyr Tyr Gln Leu Pro Thr Leu Cys
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                                     715
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Gln Gln Pro Gly Arg Cys Cys Arg Arg Asp Ala Leu Cys Asn Arg Asp
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Gln Pro Leu Gly Ser Val His Pro Val Glu Phe Gly Ser Ile Ile Thr
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Gly Glu Pro Ser Pro Pro Asn Pro Glu Glu Ser Glu Leu Thr
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     <213> Rat
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His Arg Val Tyr Val Gly Leu Phe Thr Gly Ser Ser Pro Asn Pro Phe
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                                                 30
Ala Glu Asp Val Lys Arg Pro Pro Glu Pro Leu Val Thr Asp Lys Glu
                          40
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Ala Arg Lys Lys Val Leu Lys Gln Ala Phe Ser Val Ser Arg Val Pro
                     55
Glu Lys Leu Asp Ala Val Val Ile Gly Ser Gly Ile Gly Gly Leu Ala
                  70
Ser Ala Ala Ile Leu Ala Lys Ala Gly Lys Arg Val Leu Val Leu Glu
              85
                                 90
Gln His Thr Lys Ala Gly Gly Cys Cys His Thr Phe Gly Glu Asn Gly
          100
                              105
Leu Glu Phe Asp Thr Gly Ile His Tyr Ile Gly Arg Met Arg Glu Gly
      115
                         120
                                             125
Asn Ile Gly Arg Phe Ile Leu Asp Gln Ile Thr Glu Gly Gln Leu Asp
 130
                     135
                                        140
Trp Ala Pro Met Ala Ser Pro Phe Asp Leu Met Ile Leu Glu Gly Pro
                           155.
                150
Asn Gly Arg Lys Glu Phe Pro Met Tyr Ser Gly Arg Lys Glu Tyr Ile
165 170 175
Gln Gly Leu Lys Glu Lys Phe Pro Lys Glu Glu Ala Val Ile Asp Lys
          180
                            185
                                       190
Tyr Met Glu Leu Val Lys Val Val Ala His Gly Val Ser His Ala Ile
       195
                         200
                                            205
Leu Leu Lys Phe Leu Pro Leu Pro Leu Thr Gln Leu Leu Asn Lys Phe
   210
                     215 .
                                220
Gly Leu Leu Thr Arg Phe Ser Pro Phe Cys Arg Ala Ser Thr Gln Ser
                 230 .
                                   235
Leu Ala Glu Val Leu Lys Gln Leu Gly Ala Ser Pro Glu Leu Gln Ala
             245
                                250
                                                    255
Val Leu Ser Tyr Ile Phe Pro Thr Tyr Gly Val Thr Pro Ser His Thr 260 265 270
Thr Phe Ser Leu His Ala Leu Leu Val Asp His Tyr Ile Gln Gly Ala
275 280 285
      275 .
Tyr Tyr Pro Arg Gly Gly Ser Ser Glu Ile Ala Phe His Thr Ile Pro
                     295
                                        300
Leu Ile Gln Arg Ala Gly Gly Ala Val Leu Thr Arg Ala Thr Val Gln
                 310
                                     315 .
Ser Val Leu Leu Asp Ser Ala Gly Arg Ala Cys Gly Val Ser Val Lys
              325
                                330
                                                    335
Lys Gly Gln Glu Leu Val Asn Ile Tyr Cys Pro Val Val Ile Ser Asn
           340
                              34,5
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Ala Gly Met Phe Asn Thr Tyr Gln His Leu Leu Pro Glu Ser Val Arg
       355
                        360
                                         365
Tyr Leu Pro Asp Val Lys Lys Gln Leu Thr Met Val Lys Pro Gly Leu
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                   375
                             380
Ser Met Leu Ser Ile Phe Ile Cys Leu Lys Gly Thr Lys Glu Glu Leu 385 390 395 400
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                                 395
Lys Leu Gln Ser Thr Asn Tyr Tyr Val Tyr Phe Asp Thr Asp Met Asp 405 410 415
Lys Ala Met Glu Arg Tyr Val Ser Met Pro Lys Glu Lys Ala Pro Glu
         420
                           425
                                           430
His Ile Pro Leu Leu Phe Ile Ala Phe Pro Ser Ser Lys Asp Pro Thr
               440
                                445
Trp Glu Asp Arg Phe Pro Asp Arg Ser Thr Met Thr Val Leu Val Pro
             455
Thr Ala Phe Glu Trp Phe Glu Glu Trp Gln Glu Glu Pro Lys Gly Lys
               470
                       475
Arg Gly Val Asp Tyr Glu Thr Leu Lys Asn Thr Phe Leu Glu Ala Ser
            485
                       490
                                                495
Met Ser Val Ile Met Lys Leu Phe Pro Gln Leu Glu Gly Lys Val Glu 500 505 510
                                     510
Ser Val Thr Gly Gly Ser Pro Leu Thr Asn Gln Tyr Tyr Leu Ala Ala 515 520 525
His Arg Gly Ala Thr Tyr Gly Ala Asp His Asp Leu Ala Arg Leu His
 530 . 535
                                     540
Pro His Ala Met Ala Ser Leu Arg Ala Gln Thr Pro Ile Pro Asn Leu
545 550
                          555
Tyr Leu Thr Gly Gln Asp Ile Phe Thr Cys Gly Leu Met Gly Ala Leu
           565 570 575
Gln Gly Ala Leu Leu Cys Ser Ser Ala Ile Leu Lys Arg Asn Leu Tyr
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Ser Asp Leu Gln Ala Leu Gly Ser Lys Val Arg Ala Gln Lys Lys
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Lys
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<212> PRT

<213> Rat

<400> 499

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Ser Val Arg Asp Gln Asp Ser Gly Asp Asn Gly Arg Ile Leu Cys Ser
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Ile Pro Asp Asp Leu Pro Phe Ile Leu Lys Pro Thr Phe Lys Asn Phe
               150
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Phe Thr Leu Leu Ser Glu Lys Ala Leu Asp Arg Glu Ser Arg Ala Glu
            165
                       170
                                              175
Tyr Asn Ile Thr Ile Thr Val Ser Asp Leu Gly Thr Pro Arg Leu Thr
       180 185 190
Thr Gln His Thr Ile Thr Val Gln Val Ser Asp Ile Asn Asp Asn Ala
 195
                      200
                               205
Pro Ala Phe Thr Gln Thr Ser Tyr Thr Met Phe Val His Glu Asn Asn
        215
                            220
Ser Pro Ala Leu His Ile Gly Thr Ile Ser Ala Thr Asp Ser Asp Ser
       230
                        235
Gly Ser Asn Ala His Ile Thr Tyr Ser Leu Met Pro Pro Arg Asp Pro
                            250
Gln Leu Ala Leu Asp Ser Leu Ile Ser Ile Asn Ala Asp Asn Gly Gln
         260
                           265
Leu Phe Ala Leu Arg Ala Leu Asp Tyr Glu Val Leu Gln Ala Phe Glu
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               280
Phe Arg Val Gly Ala Thr Asp Arg Gly Ser Pro Ala Leu Ser Ser Gln 290 295 300
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Ala Leu Val Arg Val Val Leu Asp Asp Asn Asp Asn Ala Pro Phe
305
            310
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Val Leu Tyr Pro Leu Gln Asn Ala Ser Ala Pro Tyr Thr Glu Leu Leu
        325 330
Pro Arg Ala Ala Glu Pro Gly Tyr Leu Val Thr Lys Val Val Ala Val 340 345 350
Asp Arg Asp Ser Gly Gln Asn Ala Trp Leu Ser Phe Gln Leu Leu Lys
     355 360
                                       365
Ala Thr Glu Pro Gly Leu Phe Ser Val Trp Ala His Asn Gly Glu Val
                   375
                                     380
Arg Thr Ser Arg Leu Leu Ser Glu Arg Asp Ala Pro Lys His Lys Leu
              390
                               395
Leu Leu Met Val Lys Asp Asn Gly Asp Pro Pro Arg Ser Ala Ser Val
405 410 415
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Met Leu His Val Leu Val Val Asp Gly Phe Ser Gln Pro Tyr Leu Pro
         420
                          425 . 430
Leu Pro Glu Val Ala His Asn Pro Ala His Asp Glu Asp Thr Leu Thr
 435
              440
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Leu Tyr Leu Val Ile Ala Leu Ala Ser Val Ser Ser Leu Phe Leu Leu 450 455 460
Ser Val Leu Leu Phe Val Gly Val Arg Leu Cys Lys Lys Ala Arg Ala
465 470
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Ala Ser Leu Gly Gly Cys Ser Val Pro Glu Gly His Phe Pro Gly His
             485
                        490
                                      495 .
Leu Val Asp Val Thr Gly Thr Gly Thr Leu Ser Gln Asn Tyr Gln Tyr
        500
                          505 510
Glu Val Cys Leu Thr Gly Ser Thr Gly Thr Asn Glu Phe Lys Phe Leu 515 520 525
      515
                       520
Lys Pro Val Met Pro Ser Leu Gln Leu Gln Asp Pro Asp Ser Asn Met
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Leu Val Lys Glu Asn Phe Arg Asn Ser Leu Gly Phe Asn Ile Gln
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<212> PRT <213> Mouse

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425

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Pro Asn Gln Glu Thr Ser Phe Tyr Leu Val Gly Asn Leu Trp Leu Met
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Ser Leu Lys Ala Leu Lys Tyr Arg Ser Met Lys Ile Thr Val Asn Ala
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Ala Leu Gln Arg Gln Phe His Ser Pro Phe Ile Phe Arg Glu Glu Asp
                 470
                                 475
Pro Ser Arg Gln Val Thr Phe Glu Ile Ser Lys Gln Glu Asp Trp Gln
     485
                               490 495
Val Pro Ile Trp Ile Ile Val Gly Ser Ser Leu Gly Gly Leu Leu Leu
         500
                        505
                                               510
Leu Ala Leu Leu Val Leu Ala Leu Trp Lys Leu Gly Phe Phe Lys Ser
      515
                        520
Ala Lys Arg Lys Arg Glu Pro Ser Leu Gly Pro Val Pro Lys Glu Leu
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Asp Ser His Ser Tyr Gln Asn Ala Arg Phe Gly Ser Cys Ile Ala Ser
                                         45
                       40
Val Gln Asp Leu Asn Gln Asp Ser Tyr Asn Asp Val Val Val Gly Ala
                     55
                                      60
Pro Leu Glu Asp Ser His Arg Gly Ala Ile Tyr Ile Phe His Gly Phe
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               70
Gln Thr Asn Ile Leu Lys Lys Pro Val Gln Arg Ile Ser Ala Ser Glu
             85
                                9.0
Leu Ala Pro Gly Leu Gln His Phe Gly Cys Ser Ile His Gly Gln Leu
          100
                           105
                                              110
Asp Leu Asn Glu Asp Gly Leu Val Asp Leu Ala Val Gly Ala Leu Gly
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                     120
                                            125
Asn Ala Val Val Leu Trp Ala Arg Pro Val Val Gln Ile Asn Ala Ser
130 135 140
Leu His Phe Glu Pro Ser Lys Ile Asn Ile Phe His Lys Asp Cys Lys
                                   155
       150
Arg Asn Gly Arg Asp Ala Thr Cys Leu Ala Ala Phe Leu Cys Phe Gly
             165
                                170
                                                  175 .
Pro Ile Phe Leu Ala Pro His Phe His Thr Ala Thr Val Gly Ile Arg
          180
                          185
                                            190
Tyr Asn Ala Thr Met Asp Glu Arg Arg Tyr Met Pro Arg Ala His Leu 195 200 205
Asp Glu Gly Ala Asp Gln Phe Thr Asn Arg Ala Val Leu Leu Ser Ser
  210
                    215
                                       220
Gly Gln Glu His Cys Gln Arg Ile Asn Phe His Val Leu Asp Thr Ala
                230
                            235
Asp Tyr Val Lys Pro Val Ala Phe Ser Val Glu Tyr Ser Leu Glu Asp
              245
                               250
                                                 255
Pro Asp His Gly Pro Met Leu Asp Asn Gly Trp Pro Thr Thr Leu Arg
```

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260
                            265
Val Ser Val Pro Phe Trp Asn Gly Cys Asn Glu Asp Glu His Cys Val
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                      280
                                         285
Pro Asp Leu Val Leu Asp Ala Arg Ser Asp Leu Pro Thr Ala Met Glu
 290
                   295
                                      300
Thr Leu Ser Phe Asp Thr Thr Val Phe Ile Ile Glu Ser Thr Arg Arg
             325
                              330 335
Arg Val Ala Val Glu Ala Thr Leu Glu Asn Arg Gly Glu Asn Ala Tyr
          340
                            345
                                              350
Ser Ala Val Leu Asn Ile Ser Gln Ser Glu Asn Leu Gln Phe Ala Ser 355 360 365
Leu Ile Gln Lys Asp Asp Ser Asp Asn Ser Ile Glu Cys'Val Asn Glu 370 380
Glu Arg Arg Leu His Lys Lys Val Cys Asn Val Ser Tyr Pro Phe Phe
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                          395
Arg Ala Lys Ala Lys Val Ala Phe Arg Leu Asp Phe Glu Phe Ser Lys
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                               410
Ser Val Phe Leu His His Leu Gln Ile His Leu Gly Ala Gly Ser Asp 420 425 430
Ser His Glu Gln Asp Ser Thr Ala Asp Asp Asn Thr Ala Leu Leu Arg
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                                445
Phe His Leu Lys Tyr Glu Ala Asp Val Leu Phe Thr Arg Ser Ser Ser
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                                      460
Leu Ser His Phe Glu Val Lys Ala Asn Ser Ser Leu Glu Ser Tyr Asp
                470
                                  475
Gly Ile Gly Pro Pro Phe Asn Cys Val Phe Lys Val Gln Asn Leu Gly
            485
                               490
Phe Phe Pro Ile His Gly Val Met Met Lys Ile Thr Val Pro Ile Ala
          500
                            505
Thr Arg Gly Gly Asn Arg Leu Leu Met Leu Lys Asp Phe Phe Thr Asp
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                      520
                                          525
Gln Val Asn Thr Ser Cys Asn Ile Trp Gly Asn Ser Thr Glu Tyr Arg
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                   535
                                      540
Ser Thr Pro Thr Glu Glu Asp Leu Ser His Ala Pro Gln Arg Asn His
545 550
                                 555
Ser Asn Ser Asp Val Val Ser Ile Ile Cys Asn Val Arg Leu Ala Pro
             565
                               570
                                              575
Asn Gln Glu Thr Ser Phe Tyr Leu Val Gly Asn Leu Trp Leu Met Ser
         580
                          585
                                             590
Leu Lys Ala Leu Lys Tyr Arg Ser Met Lys Ile Thr Val Asn Ala Ala
      595
                       600
Leu Gln Arg Gln Phe His Ser Pro Phe Ile Phe Arg Glu Glu Asp Pro
  610
                    615
                                     620
Ser Arg Gln Val Thr Phe Glu Ile Ser Lys Gln Glu Asp Trp Gln Val
               630
                                 635
Pro Ile Trp Ile Ile Val Gly Ser Ser Leu Gly Gly Leu Leu Leu Leu 645 655
Ala Leu Leu Val Leu Ala Leu Gly Ser Leu Val Ser Leu Lys Val Pro
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                   665 670
Ser Ala Arg Gly Ser Pro Ala Trp Ala Pro Ser Pro Lys Ser Trp Ser
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Glu Asp Pro Glu Glu Ala Ser Ser
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<210> 503 <211> 819 <212> PRT <213> Rat

<211> 242

<400> 503

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| Glu | Met | Asp 115 | Ser | Arg | Leu | Ala | Gln 120 | | Thr | Ser | Ala | Ser 125 | | Pro | Glu |
| Thr | Thr 130 | Val | Ala | Val | Pro | Pro 135 | Thr | Pro | Ala | Gln | Arg 140 | | Gly | Lys | Asn |
| 145 | | | Val | | 150 | | | | | 155 | | | | | 160 |
| Leu | Cys | Ser | Ala | Asp 165 | Ser | Phe | Cys | Val | Asn 170 | Asp | Tyr | Ala | Trp | Gly 175 | Gly |
| | | | His 180 | | | | | 185 | _ | _ | | | 190 | | |
| | | 195 | Ile | | | | 200 | | | | | 205 | | | |
| | 210 | | Leu | | | 215 | | | | | 220 | | | | |
| 225 | | | Glu | | 230 | | | | | 235 | | | | | 240 |
| | | | Arg | 245 | | | | | 250 | | | | | 255 | |
| | | | Arg 260 | • | | | | 265 | _ | | | | 270 | | |
| | | 275 | Ile | | | | 280 | | | | | 285 | | | |
| | 290 | | Asn | _ | | 295 | | • | | | 300 | | | | |
| 305 | | | Gln | | 310 | | | | | 315 | | | | | 320 |
| | | | Gly Gly | 325 | | | | | 330 | | | _ | | 335 | _ |
| | • | | 340 Asp | | | | | 345 | | | | | 350 | | |
| | | 355 | Ġly | | | | 360 | | | | | 365 | | | |
| | 370 | | Gly | - | | 375 | | | | | 380 | | | | |
| 385 | | | Leu | | 390 | | | | | 395 | | | | | 400 |
| | | | Pro | 405 | | | | | 410 | | | | | 415 | |
| | | | 420 Leu | | | | | 425 | | | | | 430 | | |
| Ile | Thr | 435 Phe | Arg | Pro | Asp | Ser | 440 Gly | Asp | Gly | Val | Leu | 445 Leu | Tyr | Ser | Tyr |
| | 450 | | Ser | | | 455 | | | | | 460 | | | | |
| 465 Val | Glu | Phe | Arg | Phe | 470 Asp | Cys | Gly | Ser | Gly | 475 Thr | Gly | Val | Leu | Arg | 480 Ser |
| Glu | Asp | Thr | Leu | 485 Thr | Leu | Gly | | | 490 His | Asp | Leu | Arg | Val | 495 Ser | Arg |
| Thr | Ala | | 500 Asn | G1y | Ile | Leu | Gln | 505 Val | Asp · | Lys | Gln | | 510 Val | Val | Glu |
| Gly | | 515 Ala | Glu | Gly | Gly | | 520 Thr | Gln | Ile | Lys | | 525 Asn | Thr | Asp | Ile |
| | 530 Ile | Gly | Gly | Val | | 535 Asn | Tyr | Asp | Asp | | 540 Lys | Lys | Asn | Ser | |
| 545 | | | | | 550 | | | • | | 555 | | | | | 560 |

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Ile Leu His Pro Phe Ser Gly Ser Ile Gln Lys Ile Ile Leu Asn Asp
               565
                                 570
Arg Thr Ile His Val Arg His Asp Phe Thr Ser Gly Val Asn Val Glu
          580
                             585
                                                 590
Asn Ala Ala His Pro Cys Val Gly Ala Pro Cys Ala His Gly Gly Ser
     595
                        600
                                       605
Cys Arg Pro Arg Lys Glu Gly Tyr Glu Cys Asp Cys Pro Leu Gly Phe 610 615 620
  610
                     61`5
                                        620
Glu Gly Leu Asn Cys Gln Lys Ala Ile Thr Glu Ala Ile Glu Ile Pro
                630
                                   635
Gln Phe Ile Gly Arg Ser Tyr Leu Thr Tyr Asp Asn Pro Asn Ile Leu
              645
                     650
Lys Arg Val Ser Gly Ser Arg Ser Asn Ala Phe Met Arg Phe Lys Thr
          660
                             665
Thr Ala Lys Asp Gly Leu Leu Trp Arg Gly Asp Ser Pro Met Arg 675 680 685
Pro Asn Ser Asp Phe Ile Ser Leu Gly Leu Arg Asp Gly Ala Leu Val
                                        700
                    695
  690
Phe Ser Tyr Asn Leu Gly Ser Gly Val Ala Ser Ile Met Val Asn Gly
                 710
                             715
Ser Phe Ser Asp Gly Arg Trp His Arg Val Lys Ala Val Arg Asp Gly 725 730 735
Gln Ser Gly Lys Ile Thr Val Asp Asp Tyr Gly Ala Arg Thr Gly Lys 740 745 750
                                                750
Ser Pro Gly Met Met Arg Gln Leu Asn Ile Asn Gly Ala Leu Tyr Val
     755
                        760
                                             765
Gly Gly Met Lys Glu Ile Ala Leu His Thr Asn Arg Gln Tyr Met Arg
                    775 .
                                780
Gly Leu Val Gly Cys Ile Ser His Phe Thr Leu Ser Thr Asp Tyr His 785 790 795
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Ile Ser Leu Val Glu Asp Ala Val Asp Gly Lys Asn Ile Asn Thr Cys
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Gly Ala Lys
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     <213> Human
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Glu Gln Gly His Leu Arg Ser Leu Val Leu Gly Asp Asn Cys Leu Ser
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                            25
                                              30
Glu Asn Tyr Glu Glu Thr Ala Ala Leu His Ala Leu Pro Gly Leu
     35
                        40
                                          45
Arg Arg Leu Asp Leu Ser Gly Asn Ala Leu Thr Glu Asp Met Ala Ala 50 55 60
Leu Met Leu Gln Asn Leu Ser Ser Leu Arg Ser Val Ser Leu Ala Gly
     70
Asn Thr Ile Met Arg Leu Asp Asp Ser Val Phe Glu Gly Leu Glu Arg
             85
                              90
Leu Arg Glu Leu Asp Leu Gln Arg Asn Tyr Ile Phe Glu Ile Glu Gly
     100
                           105 · 110
Gly Ala Phe Asp Gly Leu Ala Glu Leu Arg His Leu Asn
      115
                        120
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     <211> 551
     <212> PRT
     <213> Rat
     <400> 506
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Ala Gly Gly Val Gly Thr Ser Pro Arg Asp Tyr Trp Leu Pro Ala Leu
  . 20
                            25
                                              30
Ala His Gln Pro Gly Val Cys His Tyr Gly Thr Lys Thr Ala Cys Cys
     35
                        40
                                          45
Tyr Gly Trp Lys Arg Asn Ser Lys Gly Val Cys Glu Ala Val Cys Glu
                    55
                                 60
Pro Arg Cys Lys Phe Gly Glu Cys Val Gly Pro Asn Lys Cys Arg Cys
                 70
                                   75
Phe Pro Gly Tyr Thr Gly Lys Thr Cys Ser Gln Asp Val Asn Glu Cys
              85
                               90
Ala Phe Lys Pro Arg Pro Cys Gln His Arg Cys Val Asn Thr His Gly
                  105
        100
Ser Tyr Lys Cys Phe Cys Leu Ser Gly His Met Leu Leu Pro Asp Ala
     115
                     120
Thr Cys Ser Asn Ser Arg Thr Cys Ala Arg Ile Asn Cys Gln Tyr Ser
 130
                    135
                                       140
Cys Glu Asp Thr Ala Glu Gly Pro Arg Cys Val Cys Pro Ser Ser Gly 145 150 150 160
145
               150
                                155
Leu Arg Leu Gly Pro Asn Gly Arg Val Cys Leu Asp Ile Asp Glu Cys 165 170 . 175
Ala Ser Ser Lys Ala Val Cys Pro Ser Asn Arg Arg Cys Val Asn Thr
          180
                           185
                                             190
```

Phe Gly Ser Tyr Tyr Cys Lys Cys His Ile Gly Phe Glu Leu Lys Tyr 195 200 205 Ile Ser Arg Arg Tyr Asp Cys Val Asp Ile Asn Glu Cys Thr Leu Asn

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220 .-
Thr Arg Thr Cys Ser Pro His Ala Asn Cys Leu Asn Thr Gln Gly Ser
              230
                           235
Phe Lys Cys Lys Cys Lys Gln Gly Tyr Arg Gly Asn Gly Leu Gln Cys 245 250 255
Ser Val Ile Pro Glu His Ser Val Lys Glu Ile Leu Thr Ala Pro Gly 260 265 270
Thr Ile Lys Asp Arg Ile Lys Lys Leu Leu Ala His Lys His Thr Met 275 280 285
Lys Lys Lys Val Lys Leu Lys Asn Val Thr Pro Arg Pro Thr Ser Thr
  290
          295
                                300
Arg Ala Pro Lys Val Asn Leu Pro Tyr Ser Ser Glu Glu Gly Val Ser 305 310 315 320
Arg Gly Arg Asn Ser Gly Gly Glu Gln Lys Arg Lys Glu Glu Arg Lys 325 330 335
Arg Lys Arg Leu Glu Glu Glu Lys Ser Glu Lys Ala Leu Arg Asn Glu
     340 345 350
Val Glu Glu Arg Pro Leu Arg Gly Asp Val Phe Ser Pro Lys Val
       355
                        360
                                            365
Asn Glu Ala Glu Asp Leu Asp Leu Val Tyr Ile Gln Arg Lys Glu Leu
             375
                                        380
Asn Ser Lys Gln Glu His Lys Ala Asp Leu Asn Ile Ser Val Asp Cys 385 390 395 400
Ser Phe Asp Leu Gly Val Cys Asp Trp Lys Gln Asp Arg Glu Asp Asp 405 410 415
Phe Asp Trp Asn Pro Ala Asp Arg Asp Asn Asp Val Gly Tyr Tyr Met 420 425 430
Ala Val Pro Ala Leu Ala Gly His Lys Lys Asn Ile Gly Arg Leu Lys 435 440 445
Leu Leu Pro Asn Leu Thr Pro Gln Ser Asn Phe Cys Leu Leu Phe
 450 455 460
Asp Tyr Arg Leu Ala Gly Asp Lys Val Gly Lys Leu Arg Val Phe Val 465 470 475 480
Lys Asn Ser Asn Asn Ala Leu Ala Trp Glu Glu Thr Lys Thr Glu Asp
             485
                        490 495
Gly Lys Trp Lys Thr Gly Lys Val Pro Leu Tyr Gln Gly Ile Asp Thr 500 \hspace{1cm} 505 \hspace{1cm} 510
Thr Lys Ser Val Ile Phe Glu Ala Glu Arg Gly Lys Gly Lys Thr Gly
      515
                520
                                            525
Glu Ile Ala Val Asp Gly Val Leu Leu Val Ser Gly Leu Cys Pro Asp
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                  535
                             .. 540
Asp Phe Leu Ser Glu Glu Gly
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     <211> 244
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     <213> Mouse
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Tyr Ala Ser Ala Ser Glu Pro Thr Glu Ile Tyr Arg Thr Glu Leu Gln
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Gly Leu Trp Ile Asn Asp Ile Val Pro Ile Gly Arg Ile Gln Glu Pro
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                          · 25
                                              30
Ala His Leu Asp Phe Met Cys Leu Gln Asn Glu Val Tyr Lys Gln Thr
                         40
                                         . 45
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Glu Gln Leu Ala Glu Leu Ser Lys Gly Val Gln Glu Val Val Leu Ser

```
55
Ser Ile Leu Ser Met Leu Tyr Glu Gly Asp Arg Lys Val Leu Tyr Asp
                                    75
           70
Leu Met Asn Met Leu Glu Leu Asn Gln Leu Gly His Met Asp Gly Pro
                          90
             85
Gly Gly Lys Ile Leu Asp Glu Leu Arg Lys Asp Ser Ser Asn Pro Cys
100 105 110
                                     110
                          105
Val Asp Leu Lys Asp Leu Ilè Leu Tyr Leu Leu Gln Ala Leu Met Val
    115
                       120
                                   125
Leu Ser Asp Ser Gln Leu Asn Leu Leu Ala Gln Ser Val Glu Met Gly
                     135
  130
                                        140
Ile Leu Pro His Gln Val Glu Leu Val Lys Ser Ile Leu Gln Pro Asn
                150
                                   155
Phe Lys Tyr Pro Trp Asn Ile Pro Phe Thr Val Gln Pro Gln Leu Leu
165 170 175
             165
Ala Pro Leu Gln Gly Glu Gly Leu Ala Ile Thr Tyr Glu Leu Leu Glu
          180
                          185
                                              190
Glu Cys Gly Leu Lys Met Glu Leu Asn Asn Pro Arg Ser Thr Trp Asp
                200
                               . 205
     195
Leu Glu Ala Lys Met Pro Leu Ser Ala Leu Tyr Gly Ser Leu Ser Phe 210 215 220
Leu Gln Gln Leu Arg Lys Ala Asn Ser Ser Ser Lys Pro Ser Leu Arg
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                                 235
225
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Pro Gly Tyr Ile
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<210> 508 <211> 248 <212> PRT

<213> Human

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Gln Ser Leu Tyr Ile Val Tyr Ile Ala Leu Pro Gly Arg Thr Pro Arg 65 70 75 80

Pro Ala Leu Ala Phe Ala Phe Leu Met Pro Ala Cys Cys Asn Arg Pro

Pro Ala Leu Ala Phe Ala Phe Leu Met Pro Ala Cys Cys Asn Arg Pro 85 90 95 Ser Pro Arg Pro Ser Pro Ala His Leu Thr Ala Ser Ser Val Leu Arg

100 105 110 , Arg Gln Arg His Val Leu Ala Ala Ser Ala Ala Ser Pro Cys Gln Trp

115 120 125 Ser Gly Leu Arg Val Ala His Ser Leu Arg Gln Val Val Ser Leu Cys 130 135 140

Pro Arg Cys Thr Gly Ser Cys Pro Phe Ser Gly Ala Cys Ala Ser Ser 145 150 155 160

Leu Pro Ser Pro Leu Ser Cys Pro His Ser His Ser Gly Ser Trp Gly
165 170 175

Thr Trp Ser Gln Gly Arg Pro Cys Ser Ser Thr Glu Val Ala Gly Leu 180 185 190 Ala Leu Trp Pro Thr Asp Phe Leu Ser Cys Leu Leu Asp Ala Ser Glu

200

205

```
Leu Gln Thr Gln Gly Ser His Gly Phe Ser Phe Thr Pro Thr Gly Phe
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                                    220
Ser Ser Asn Arg Lys Val Gly Val Gly Ser Cys Arg Asp Gly Ala Gly
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                                  235
Arg Gly Ala Met Gly Gly Leu Phe
             245
     <210> 509
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     <213> Mouse
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Met Pro Val Ser Trp Phe Leu Leu Ser Leu Ala Leu Gly Arg Asn Pro
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Val Val Val Ser Leu Glu Arg Leu Met Glu Pro Gln Asp Thr Ala Arg
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                           25
Cys Ser Leu Gly Leu Ser Cys His Leu Trp Asp Gly Asp Val Leu Cys
                     40
    35
                                         45
Leu Pro Gly Ser Leu Gln Ser Ala Pro Gly Pro Val Leu Val Pro Thr
          55 60
Arg Leu Gln Thr Glu Leu Val Leu Arg Cys Pro Gln Lys Thr Asp Cys
65 70
                              75
Ala Leu Cys Val Arg Val Val His Leu Ala Val His Gly His Trp
                                                95
            85
                              90
Ala Glu Pro Glu Glu Ala Gly Lys Ser Asp Ser Glu Leu Gln Glu Ser
         . 100
                           105
                                            110
Arg Asn Ala Ser Leu Gln Ala Gln Val Val Leu Ser Phe Gln Ala Tyr
                        120
                                          125
Pro Ile Ala Arg Cys Ala Leu Leu Glu Val Gln Val Pro Ala Asp Leu
                   135
                                     140
Val Gln Pro Gly Gln Ser Val Gly Ser Ala Val Phe Asp Cys Phe Glu
            150
                                155
Ala Ser Leu Gly Ala Glu Val Gln Ile Trp Ser Tyr Thr Lys Pro Arg
165 170 175
Tyr Gln Lys Glu Leu Asn Leu Thr Gln Gln Leu Pro Asp Cys Arg Gly
         180 185 190
Leu Glu Val Arg Asp Ser Ile Gln Ser Cys Trp Val Leu Pro Trp Leu
     195
                    200
                                         205
Asn Val Ser Thr Asp Gly Asp Asn Val Leu Leu Thr Leu Asp Val Ser
                            . 220
  210
          215
Glu Glu Gln Asp Phe Ser Phe Leu Leu Tyr Leu Arg Pro Val Pro Asp 225 230 230 235
Ala Leu Lys Ser Leu Trp Tyr Lys Asn Leu Thr Gly Pro Gln Asn Ile
            245 . 250
Thr Leu Asn His Thr Asp Leu Val Pro Cys Leu Cys Ile Gln Val Trp
         260
                         265
                                            270
Ser Leu Glu Pro Asp Ser Glu Arg Val Glu Phe Cys Pro Phe Arg Glu
275 280 285
      275
                       280
                                         285
Asp Pro Gly Ala His Arg Asn Leu Trp His Ile Ala Arg Leu Arg Val
          295
                             300
 290
Leu Ser Pro Gly Val Trp Gln Leu Asp Ala Pro Cys Cys Leu Pro Gly
               310
                              315
Lys Val Thr Leu Cys Trp Gln Ala Pro Asp Gln Ser Pro Cys Gln Pro
             325
                      330
Leu Val Pro Pro Val Pro Gln Lys Asn Ala Thr Val Asn Glu Pro Gln
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340
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 Asp Phe Gln Leu Val Ala Gly His Pro Asn Leu Cys Val Gln Val Ser
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                                         365
 Thr Trp Glu Lys Val Gln Leu Gln Ala Cys Leu Trp Ala Asp Ser Leu
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    370
                              380
 Gly Pro Phe Lys Asp Asp Met Leu Leu Val Glu Met Lys Thr Gly Leu
 385 390
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 Asn Asn Thr Ser Val Cys Ala Leu Glu Pro Ser Gly Cys Thr Pro Leu
            405
                               410
 Pro Ser Met Ala Ser Thr Arg Ala Ala Arg Leu Gly Glu Glu Leu Leu
         420
                          425
                                    430
 Gln Asp Phe Arg Ser His Gln Cys Met Gln Leu Trp Asn Asp Asp Asn
                                 445
       435
                        440
 Met Gly Ser Leu Trp Ala Cys Pro Met Asp Lys Tyr Ile His Arg Arg
                   455
                                    460
 Trp Val Leu Val Trp Leu Ala Cys Leu Leu Leu Ala Ala Ala Leu Phe
                 470
                                  475
 Phe Phe Leu Leu Lys Lys Asp Arg Arg Lys Ala Ala Arg Gly Ser
            485
                             490
                                        495
 Arg Thr Ala Leu Leu His Ser Ala Asp Gly Ala Gly Tyr Glu Arg
          500
                            505
 Leu Val Gly Ala Leu Ala Ser Ala Leu Ser Gln Met Pro Leu Arg Val
      515
                     520
                                         525
 Ala Val Asp Leu Trp Ser Arg Arg Glu Leu Ser Ala His Gly Ala Leu
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                535
                              540
 Ala Trp Phe His His Gln Arg Arg Ile Leu Gln Glu Gly Gly Val
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               550
                                  555
 Val Ile Leu Leu Phe Ser Pro Ala Ala Val Ala Gln Cys Gln Gln Trp
            565
                              570 575
Leu Gln Leu Gln Thr Val Glu Pro Gly Pro His Asp Ala Leu Ala Ala
          580
                          585
                                           590
 Trp Leu Ser Cys Val Leu Pro Asp Phe Leu Gln Gly Arg Ala Thr Gly
                       600
                                         605
 Arg Tyr Val Gly Val Tyr Phe Asp Gly Leu Leu His Pro Asp Ser Val
    610
                     615
                                      620
 Pro Ser Pro Phe Arg Val Ala Pro Leu Phe Ser Leu Pro Ser Gln Leu
        630
                                 635
 Pro Ala Phe Leu Asp Ala Leu Gln Gly Gly Cys Ser Thr Ser Ala Gly
           645
                               650
Arg Pro Ala Asp Arg Val Glu Arg Val Thr Gln Ala Leu Arg Ser Ala
660 665 670
          660
                           665
                                            670
Leu Asp Ser Cys Thr Ser Thr Ser Glu Ala Pro Gly Cys Cys Glu Glu
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                                          685
 Trp Asp Leu Gly Pro Cys Thr Thr Leu Glu
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tagetetega tgtettetgt caagttatgg eteaatggtg egteategat etetetegtg
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cgggcacgcc acacagcatg gaaccttgat gtagcagtca agatcgtgaa ctcgaagaag

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                                                                       420
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                                                                       540
togetactge accgggacet caagecetee aatgttetge tggatecaga getecaegee
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aagttagcag actttggcct gtccacattt cagggagggt cacagtcagg gtcagggtca
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                                                                       780
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                                                                      1080
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                                                                      1140
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Pro Leu Glu Asp Ser His Arg Gly Ala Ile Tyr Ile Phe His Gly Phe
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Gln Thr Asn Ile Leu Lys Lys Pro Val Gln Arg Ile Ser Ala Ser Glu
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Leu Ala Pro Gly Leu Gln His Phe Gly Cys Ser Ile His Gly Gln Leu
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                70
                           · 75
Asp Gln Phe Cys Val Asn Thr Glu Gly Ser Tyr Glu Cys Arg Asp Cys
            85
                              90
Ala Lys Ala Cys Leu Gly Cys Met Gly Ala Gly Pro Gly Arg Cys Lys 100 105 110
Lys Cys Ser Arg Gly Tyr Gln Gln Val Gly Ser Lys Cys Leu Asp Val
     115
                     120
                                      125
Asp Glu Cys Glu Thr Val Val Cys Pro Gly Glu Asn Glu Gln Cys Glu
  130
                   135
                                     140
Asn Thr Glu Gly Ser Tyr Arg Cys Val Cys Ala Glu Gly Phe Arg Gln
              150
                                 155
Glu Asp Gly Ile Cys Val Lys Glu Gln Ile Pro Glu Ser Ala Gly Phe
165 170 175
Phe Ala Glu Met Thr Glu Asp Glu Met Val Val Leu Gln Gln Met Phe
         180
                          185 · 190
Phe Gly Val Ile Ile Cys Ala Leu Ala Thr Leu Ala Ala Lys Gly Asp
 195 200
                            205,
Leu Val Phe Thr Ala Ile Phe Ile Gly Ala Val Ala Ala Met Thr Gly 210 215 220
Tyr Trp Leu Ser Glu Arg Ser Asp Arg Val Leu Glu Gly Phe Ile Lys
                230
                                  235
                                                    240
Gly Arg
<210> 626
<211> 576
<212> PRT
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<213> Rat

<400> 626 Met Pro Phe Arg Leu Leu Ile Pro Leu Gly Leu Val Cys Val Leu Leu . 10 . 5 Pro Leu His His Gly Ala Pro Gly Pro Glu Gly Thr Ala Pro Asp Pro Ala His Tyr Arg Glu Arg Val'Lys Ala Met Phe Tyr His Ala Tyr Asp Ser Tyr Leu Glu Asn Ala Phe Pro Tyr Asp Glu Leu Arg Pro Leu Thr Cys Asp Gly His Asp Thr Trp Gly Ser Phe Ser Leu Thr Leu Ile Asp Ala Leu Asp Thr Leu Leu Ile Leu Gly Asn Thr Ser Glu Phe Gln Arg Val Val Glu Val Leu Gln Asp Asn Val Asp Phe Asp Ile Asp Val Asn Ala Ser Val Phe Glu Thr Asn Ile Arg Val Val Gly Gly Leu Leu Ser Ala His Leu Leu Ser Lys Lys Ala Gly Val Glu Val Glu Ala Gly Trp 130 135 140 Pro Cys Ser Gly Pro Leu Leu Arg Met Ala Glu Glu Ala Ala Arg Lys Leu Leu Pro Ala Phe Gln Thr Pro Thr Gly Met Pro Tyr Gly Thr Val Asn Leu Leu His Gly Val Asn Pro Gly Glu Thr Pro Val Thr Cys Thr Ala Gly Ile Gly Thr Phe Ile Val Glu Phe Ala Thr Leu Ser Ser Leu . 200 Thr Gly Asp Pro Val Phe Glu Asp Val Ala Arg Val Ala Leu Met Arg 210 215 Leu Trp Glu Ser Arg Ser Asp Ile Gly Leu Val Gly Asn His Ile Asp Val Leu Thr Gly Lys Trp Val Ala Gln Asp Ala Gly Ile Gly Ala Gly Val Asp Ser Tyr Phe Glu Tyr Leu Val Lys Gly Ala Ile Leu Leu Gln 260 265 270 Asp Lys Lys Leu Met Ala Met Phe Leu Glu Tyr Asn Lys Ala Ile Arg Asn Tyr Thr His Phe Asp Asp Trp Tyr Leu Trp Val Gln Met Tyr Lys 290 295 300 Gly Thr Val Ser Met Pro Val Phe Gln Ser Leu Glu Ala Tyr Trp Pro Gly Leu Gln Ser Leu Ile Gly Asp Ile Asp Asn Ala Met Arg Thr Phe Leu Asn Tyr Tyr Thr Val Trp Lys Gln Phe Gly Gly Leu Pro Glu Phe _350 Tyr Asn Ile Pro Gln Gly Tyr Thr Val Glu Lys Arg Glu Gly Tyr Pro Leu Arg Pro Glu Leu Ile Glu Ser Ala Met Tyr Leu Tyr Arg Ala Thr Gly Asp Pro Thr Leu Leu Glu Leu Gly Arg Asp Ala Val Glu Ser Ile 395 . 400 Glu Lys Ile Ser Lys Val Glu Cys Gly Phe Ala Thr Ile Lys Asp Leu Arg Asp His Lys Leu Asp Asn Arg Met Glu Ser Phe Phe Leu Ala Glu

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Thr Val Lys Tyr Leu Tyr Leu Leu Phe His Pro Asn Asn Phe Ile His
      435
                       440
                                            445
Asn Asn Gly Ser Thr Phe Asp Ser Val Met Thr Pro His Gly Glu Cys
  450
                   455
                                      460
Ile Leu Gly Ala Gly Gly Tyr Ile Phe Asn Thr Glu Ala His Pro Ile
                          475
               470
Asp Pro Ala Ala Leu His Cys Cys Arg Arg Leu Lys Glu Glu Gln Trp 485 490 495
Glu Val Glu Asp Leu Ile Lys Glu Phe Tyr Ser Leu Arg Gln Ser Arg
          500
                            505
                                      510
Ser Arg Ala Gln Arg Lys Thr Val Ser Ser Gly Pro Trp Glu Pro Pro
      515
                520
                                  525
Ala Gly Pro Gly Thr Leu Ser Ser Pro Glu Asn Gln Pro Arg Glu Lys
530 535 540
Gln Pro Ala Arg Gln Arg Ala Pro Leu Leu Ser Cys Pro Ser Gln Pro
545 550
                          555
Phe Thr Ser Lys Leu Ala Leu Leu Gly Gln Val Phe Leu Asp Ser Ser
              565
                                570
<210> 627
<211> 226
<212> PRT
<213> Rat
<400> 627
Arg Lys Ile Lys Asn Lys Ile Ser Ala Gln Glu Ser Arg Arg Lys Lys
              5
                               10
Lys Glu Tyr Val Glu Cys Leu Glu Lys Lys Val Glu Thr Tyr Thr Ser
 20
                  25
                                            30
Glu Asn Asn Glu Leu Trp Lys Lys Val Glu Thr Leu Glu Thr Ala Asn
    35
                        40
                                           45
Arg Thr Leu Leu Gln Gln Leu Gln Lys Leu Gln Thr Leu Val Thr Ser
               55
                                       60
Lys Ile Ser Arg Pro Tyr Lys Met Ala Ala Thr Gln Thr Gly Thr Cys 65 70 75 80
Leu Met Val Ala Ala Leu Cys Phe Val Leu Val Leu Gly Ser Leu Ala
             85
                               90
                                                95
Pro Cys Leu Pro Ala Phe Ser Ser Gly Ser Lys Thr Val Lys Glu Asp
         100
                            105
                                              110
Pro Val Ala Ala Asp Ser Val Tyr Ala Ala Ser Gln Met Pro Ser Arg
      115
                       120
                                   125
Ser Leu Leu Phe Tyr Asp Asp Gly Ala Gly Ser Trp Glu Asp Gly His
130 135 140
Arg Gly Ala Leu Leu Pro Val Glu Pro Pro Glu Gly Trp Glu Leu Lys
145
               150
                                   155
Pro Gly Gly Pro Ala Glu Pro Arg Pro Gln Asp His Leu Arg His Asp
                      170 _. 175
            165
His Ala Asp Ser Ile His Glu Thr Thr Lys Tyr Leu Arg Glu Thr Trp
180 185 190
                  185
Pro Glu Asp Thr Glu Asp Asn Gly Ala Ser Pro Asn Phe Ser His Pro
      195
                       200 205
Lys Glu Trp, Phe His Asp Arg Asp Leu Gly Pro Asn Thr Thr Ile Lys
  210
                     215
Leu Ser
225
```

<210> 628

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<211> 82
<212> PRT
<213> Rat
<400> 628
Pro Ile Thr Leu Ser Cys Gln Ser Gly Asn Ala Ala Ser Leu Gln Pro
1
           5
                                10
Leu His Phe Pro Pro Val Prò Pro Glu Ala Cys Pro Cys Ala Phe Arg
 20
                            25
Leu Arg Pro Phe Cys Leu His Thr Gly Cys Ala Gly Cys Ser Leu Arg
  35
                       40
Ala Ala Thr Glu Gln Cys Ala Val Ala Leu Ala Pro Gln Leu Pro. Ser
 50
                    55
                                      60
Ala Ser Arg Ala Phe Pro Pro Leu Thr Leu Cys Asn Pro Cys Val Leu
65 70
Thr Arg
<210> 629
<211> 242
<212> PRT
<213> Rat
<400> 629
Met Ala Gly Ala Gly Pro Val Leu Ser Ile Leu Gly Leu Leu Leu Val
                       10
Ser Ala Leu Phe Gly Val Leu Gly Glu Arg Pro Asn Pro Asp Leu Gly
                            25
Ala His Pro Glu Arg Arg Ser Gln Val Gly Pro Gly Ala Thr Glu Pro
     35
                       40
Arg Arg Gln Pro Pro Pro Lys Asp Gln Arg Glu Arg Ala Arg Ala Gly
                 55
 50
Ser Leu Ser Leu Gly Ala Leu Tyr Thr Ala Ala Ile Val Ala Phe Val
                70
65
                                  75
Leu Phe Lys Cys Leu Gln Gln Gly Pro Asp Glu Ala Ala Val Pro Arg
            85
                              90
Glu Glu Lys Asn Lys Lys Ser Ser Gln Ser Glu Gln Gln Leu Val
         1.00
                           105
                                            110
Gln Leu Thr Gln Gln Leu Ala Gln Thr Glu Glu His Leu Asn Asn Leu
     115
               120
                                       125
Met Thr Gln Leu Asp Pro Leu Phe Glu Arg Val Thr Thr Leu Val Gly
   130
                   135
                                    140
Thr Gln Arg Glu Leu Leu Asn Ala Lys Leu Lys Thr Ile His His Leu
               150
                       155
Leu Gln Asp Cys Lys Pro Gly Ile Gly Val Glu Ala Pro Glu Pro Glu
             165
                               170
                                                175
Ala Pro Ile His Phe Pro Glu Asp Leu Gly Lys Glu Asp. Gln Glu Asp
         180
                           185
Ala Gly Asn Ser Gln Ala Trp Glu Glu Pro Ile Asn Trp Ser Ser Glu
     195
                       200
                                         205
Thr Trp Asn Leu Ala Pro Ser Trp Glu Val Glu Gln Gly Leu Arg Arg
                    215
 210
                                     220
Arg Trp His Lys Thr Lys Gly Pro Ala Val Asn Gly Gly Gln Ala Leu
                                  235
                230
Lys Val
```

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<210> 630
<211> 289
<212> PRT
<213> Rat
<400> 630
Met Ile Val Leu Leu Tyr Val Thr Ser Leu Ala Ile Cys Ala Ser Gly
             5
 1
                                  10
Gln Pro Arg Gly Asn Gln Ala Lys Gly Glu Ser Tyr Ser Pro Arg Tyr
          20
                              25
Ile Cys Ser Ile Pro Gly Leu Pro Gly Pro Pro Gly Pro Pro Gly Ala
                          40
Asn Gly Ser Pro Gly Pro His Gly Arg Ile Gly Leu Pro Gly Arg Asp
                     55
                                         60
Gly Arg Asp Gly Arg Lys Gly Glu Lys Gly Glu Lys Gly Thr Ala Gly
                  70
                                    75
Leu Lys Gly Lys Thr Gly Pro Leu Gly Leu Ala Gly Glu Lys Gly Asp
              85
                                 90
                                                    95
Gln Gly Glu Thr Gly Lys Lys Gly Pro Ile Gly Pro Glu Gly Glu Lys
                             105
          100
                                               110
Gly Glu Val Gly Pro Ala Gly Pro Pro Gly Pro Lys Gly Asp Arg Gly
     115
                         120
                                            125
Asp Gln Gly Asp Pro Gly Leu Pro Gly Val Cys Arg Cys Gly Ser Ile
  130
                     135
                                        140
Val Leu Lys Ser Ala Phe Ser Val Gly Ile Thr Thr Ser Tyr Pro Glu
                 150
                                    155
                                                        160
Glu Arg Leu Pro Ile Ile Phe Asn Lys Val Leu Phe Asn Glu Gly Glu
165 170 175
             165
                                170
                                                   175
His Tyr Asn Pro Ala Thr Gly Lys Phe Ile Cys Ala Phe Pro Gly Ile
                             185
                                        190
Tyr Tyr Phe Ser Tyr Asp Ile Thr Leu Ala Asn Lys His Leu Ala Ile
   195
                          200
                                           205
Gly Leu Val His Asn Gly Gln Tyr Arg Ile Arg Thr Phe Asp Ala Asn
  210
                     215
                                       220
Thr Gly Asn His Asp Val Ala Ser Gly Ser Thr Val Ile Tyr Leu Gln 225 230 235
225
                  230
                                     235
                                                        240
Pro Glu Asp Glu Val Trp Leu Glu Ile Phe Phe Asn Asp Gln Asn Gly
            245
                                250
Leu Phe Ser Asp Pro Gly Trp Ala Asp Ser Leu Phe Ser Gly Phe Leu
        260
                            265
                                                270
Leu Tyr Val Asp Thr Asp Tyr Leu Asp Ser Ile Ser Glu Asp Asp Glu
                          280
                                             285
Leu
<210> 631
<211> 213
<212> PRT
<213> Rat
<400> 631
Met Val Leu Gly Gly Cys Pro Val Ser Tyr Leu Leu Leu Cys Gly Gln
                                10
                                                    15
Ala Ala Leu Leu Gly Asn Leu Leu Leu His Cys Val Ser Arg
         20
                            25
                                               30
Ser His Ser Phe Asn Ala Thr Ala Glu Leu Asp Leu Thr Pro Ser Gly
       35
                          40
```

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Ala Ala His Leu Glu Gly Pro Ala Ala Ser Ser Trp Glu Tyr Ser Asp
                     55
                                    60
Pro Asn Ser Pro Val Ile Leu Cys Ser Tyr Leu Pro Asp Glu Phe Val
                  70
                                  75
Asp Cys Asp Ala Pro Val Asp His Val Gly Asn Ala Thr Ala Tyr Gln
             85
                              90
Glu Leu Gly Tyr Gly Cys Leu Lys Phe Gly Gly Gln Ala Tyr Ser Asp
          100
                          105
                                             110
Val Glu His Thr Ala Val Gln Cys Arg Ala Leu Glu Gly Ile Glu Cys
     115
                    120
                                         125
Ala Ser Pro Arg Thr Phe Leu Arg Lys Asn Lys Pro Cys Ile Lys Tyr
                              140
 130
        135
Thr Gly His Tyr Phe Ile Thr Thr Leu Leu Tyr Ser Phe Phe Leu Gly 145 150 150 160
Cys Phe Gly Val Asp Arg Phe Cys Leu Gly His Thr Gly Thr Ala Val
            165 170 175
Gly Lys Leu Leu Thr Leu Gly Gly Leu Gly Ile Trp Trp Phe Val Asp
       180
                        185
                                    190
Leu Ile Leu Leu Ile Thr Gly Gly Leu Met Pro Ser Asp Gly Ser Asn
    195
                        200
                                          205
Trp Cys Thr Val Tyr
  210
<210> 632
<211> 167
<212> PRT
<213> Rat
<400> 632
Met Ala Ser Pro Arg Thr Ile Thr Ile Val Ala Leu Ser Val Ala Leu
              5
                              10
                                               15 .
Gly Leu Phe Phe Val Phe Met Gly Thr Ile Lys Leu Thr Pro Arg Leu
      20
                           25
                                             30
Ser Lys Asp Ala Tyr Ser Glu Met Lys Arg Ala Tyr Lys Ser Tyr Val 35 40 45
Arg Ala Leu Pro Leu Leu Lys Lys Met Gly Ile Asn Ser Ile Leu Leu
 50 55
                                    60
Arg Lys Ser Ile Gly Ala Leu Glu Val Ala Cys Gly Ile Val Met Thr
65
              70
                                  75
Leu Val Pro Gly Arg Pro Lys Asp Val Ala Asn Phe Phe Leu Leu Leu
            85
                             90
Leu Val Leu Ala Val Leu Phe Phe His Gln Leu Val Gly Asp Pro.Leu
         100
                           105
                                             110
Lys Arg Tyr Ala His Ala Leu Val Phe Gly Ile Leu Leu Thr Cys Arg
      115
              120
                                   125
Leu Leu Ile Ala Arg Lys Pro Glu Asp Arg Ser Phe Glu Lys Lys Ala
 130
                   135
                                   140 - '
Leu Pro Glu Ser Ala Glu Glu Gln Pro Ser Leu Tyr Glu Lys Ala Pro
145
              150
Gln Gly Lys Val Lys Val Ser
              165
<210> 633
<211> 138
<212> PRT
<213> Rat
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<400> 633
Phe Ile Arg Gly Met Leu Lys Leu Ile Leu Leu Leu Phe Ser Gly
                               10 ·
Ala Thr Leu Ser Ser Thr Trp Phe Thr Leu Thr Cys Leu Asn Ser Val
          20
                            25
                                          . 30
Thr His Leu Pro Leu Thr Thr Val Thr Leu Tyr Ala Ser Cys Ile Leu
      35
                       40
                                         45
Leu Gly Val Phe Leu Asn Ser Ser Val Pro Ile Phe Phe Glu Leu Phe
  50
                55
Val Glu Thr Val Tyr Pro Val Pro Glu Gly Ile Thr Cys Gly Val Val
               70 ·
                                   75
Thr Phe Leu Ser Asn Met Phe Met Gly Val Leu Leu Phe Phe Val Thr
                               90
              85
Phe Tyr His Thr Glu Leu Ser Trp Phe Asn Trp Cys Leu Pro Gly Ser
       100 105 110
Cys Leu Leu Ser Leu Leu Leu Ile Leu Cys Phe Arg Glu Ser Tyr Asp
   115
                      120
Arg Leu Tyr Leu Asp Val Val Val Ser Val
                   135
<210> 634
<211> 75
<212> PRT
<213> Rat
<400> 634 ·
Met Ile Gly Asp Ile Leu Leu Phe Gly Thr Leu Leu Met Asn Ala Gly
               5
                  10
Ala Val Leu Asn Phe Lys Leu Lys Lys Lys Asp Thr Gln Gly Phe Gly
         20
                           25
                                            30
Glu Glu Ser Arg Glu Pro Ser Thr Gly Asp Asn Ile Arg Glu Phe Leu
     35
                        40
                                          45
Leu Ser Leu Arg Tyr Phe Arg Ile Phe Ile Ala Leu Trp Asn Val Phe
 50
                   55
Met Met Leu Cys Met Ile Val Leu Phe Gly Ser
65 .
                  70
<210> 635
<211> 186
<212> PRT
<213> Rat
<400> 635
Met Val Ala Ala Val Ala Thr Ala Trp Leu Leu Trp Ala Ala Ala
              5
                               10
Cys Thr Gln Ser Glu Gln Asp Phe Tyr Asp Phe Lys Ala Val Asn Ile
       20
                           25
Arg Gly Lys Leu Val Ser Leu Glu Lys Tyr Arg Gly Ser Val Ser Leu
      35
                        40
                                          45
Val Val Asn Val Ala Ser Glu Cys Gly Phe Thr Asp Gln Asn Tyr Arg
                    55
                                 60
Ala Leu Gln Gln Leu Gln Arg Asp Leu Gly Pro Tyr His Phe Asn Val
                 70
                                   75
Leu Ala Phe Pro Cys Asn Gln Phe Gly Gln Glu Pro Asp Ser Asn
             85
                              90
Arg Glu Ile Glu Asn Phe Ala Arg Arg Thr Tyr Ser Val Ser Phe Pro
          100
                            105,
                                              110
```

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Met Phe Ser Lys Ile Ala Val Thr Gly Thr Gly Ala His Pro Ala Phe
     115
                     120
                                      125
Lys Tyr Leu Thr Gln Thr Ser Gly Lys Glu Pro Thr Trp Asn Phe Trp
 130
                   135
                                    140
Lys Tyr Leu Val Ala Pro Asp Gly Lys Val Val Gly Ala Trp Asp Pro
145
               150
                          155
                                                 160
Thr Val Pro Val Glu Glu Ile Lys Pro Arg Ile Thr Glu Gln Val Met
165 170 175
Lys Leu Ile Leu Gln Lys Arg Glu Asp Leu
        180
                         185
<210> 636
<211> 930
<212> PRT
<213> Rat
<400> 636
Met Pro Ser Leu Leu Ser Leu Val Leu Thr Phe Leu Ala Val Ser Ser
          5
                     10
Pro Ser Cys Cys Gln Asn Ser Asp Thr Ala Ser Pro Lys Ala Ser Asn
20 25 30
                          25
Gly Ala Ser Phe Leu Trp Asn Asn Met Arg Leu Pro Glu Tyr Ile Thr
    35 40 45
Pro Ile His Tyr Asp Leu Met Ile His Ala Asn Leu Ser Thr Leu Thr
                 55
                           · 60
Phe Trp Gly Lys Thr Glu Val Glu Ile Thr Val Ser Gln Pro Thr Ser
              70
                        75
Thr Ile Ile Met His Ser His Gln Leu Gln Ile Ser Lys Ala Thr Leu
            85
                            90 95
Arg Arg Gly Ala Glu Glu Met Leu Pro Glu Glu Pro Leu Lys Leu Met
        100
                        105
                                         110
Glu Tyr Ser Ala His Glu Gln Val Ala Leu Leu Thr Ala Gln Pro Leu
 115
               120
                                       125
Leu Ala Gly Ser Val Tyr Thr Val Ile Ile Thr Tyr Ala Ala Asn Leu
          135 140
 130
Ser Glu Asn Phe His Gly Phe Tyr Lys Ser Thr Tyr Arg Thr Gln Glu
145 150
                        155
Gly Glu Arg Arg Ile Leu Ala Ala Thr Gln Phe Glu Pro Thr Ala Ala
             165
                            170
                                            175
Arg Met Ala Phe Pro Cys Phe Asp Glu Pro Ala Leu Lys Ala Ser Phe
        180
                 185 190
Ser Ile Lys Ile Lys Arg Asp Pro Arg His Leu Ala Ile Ser Asn Met
     195
                      200
                              205
Pro Leu Val Lys Ser Val Thr Val Ala Glu Gly Leu Ile Glu Asp His
  210
            215
                            220
Phe Asp Ile Thr Val Lys Met Ser Thr Tyr Leu Val Ala Phe Ile Ile
225
              230
                                235
Ser Asp Phe Lys Ser Val Ser Lys Met Thr Lys Ser Gly Val Lys Val 245 250 255
Ser Val Tyr Ala Val Pro Asp Lys Ile Asn Gln Ala Asp Tyr Ala Leu
        260 265 270
Asp Ala Ala Val Thr Leu Leu Glu Phe Tyr Glu Asp Tyr Phe Ser Ile
      275 ·
             280 . 285
Pro Tyr Pro Leu Pro Lys Gln Asp Leu Ala Ala Ile Pro Asp Phe Gln
 290
           295 300
Ser Gly Ala Met Glu Asn Trp Gly Leu Thr Thr Tyr Arg Glu Ser Ala
305
                         , 315
```

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Leu Leu Tyr Asp Lys Glu Lys Ser Ser Ala Ser Ser Lys Leu Gly Ile
               325
                                      · 335
                                330
Thr Met Thr Val Ser His Glu Leu Ala His Gln Trp Phe Gly Asn Leu
           340
                          345
                                              350
Val Thr Met Glu Trp Trp Asn Asp Leu Trp Leu Asn Glu Gly Phe Ala
                        360
                                     365
Lys Phe Met Glu Phe Val Ser Val Thr Val Thr His Pro Glu Leu Lys
                     375
                                        380
Val Glu Glu Tyr Phe Phe Gly Lys Cys Val Asn Ala Met Glu Val Asp
              390
                                   395
Ala Leu Asn Ser Ser His Pro Val Ser Thr Pro Val Glu Asn Pro Ala
              405
                             410
Gln Ile Arg Glu Met Phe Asp Glu Val Ser Tyr Glu Lys Gly Ala Cys
                 . 425
          420
Ile Leu Asn Met Leu Arg Asp Tyr Leu Ser Ala Asp Thr Phe Lys Arg
     435
                        440
                                            445
Gly Ile Val Gln Tyr Leu Gln Lys Tyr Ser Tyr Lys Asn Thr Lys Asn
  450
                   455
                                       460
Glu Asp Leu Trp Asn Ser Met Met His Ile Cys Pro Thr Asp Gly Thr
               470
                                    475
Gln Thr Met Asp Gly Phe Cys Ser Arg Asn Gln His Ser Ser Ser Thr 485 490 495
              485
                              490
Ser His Trp Arg Gln Glu Val Ile Asp Ile Lys Ser Met Met Asn Thr
         500
                          505 . 510
Trp Thr Leu Gln Lys Gly Phe Pro Leu Ile Thr Ile Thr Val Arg Gly
                        520
                                           525
Arg Asn Val His Leu Lys Gln Glu His Tyr Met Lys Gly Ser Glu Cys
            535
                                       540
Phe Pro Glu Thr Gly Ser Leu Trp His Val Pro Leu Thr Phe Ile Thr 545 550 555 . 560
                                     555 .
Ser Lys Ser Asp Ser Val Gln Arg Phe Leu Leu Lys Thr Lys Thr Asp
              565
                                570
                                                    575
Val Ile Ile Leu Pro Glu Ala Val Glu Trp Ile Lys Phe Asn Val Gly
                                       . 590
         580
                           585
Met Asn Gly Tyr Tyr Ile Val His Tyr Gly Asp Asp Gly Trp Ala Ser 595 600 605
                                           605
Leu Asn Gly Leu Leu Lys Glu Ala His Thr Thr Ile Ser Ser Asn Asp
                    615
                                      620
Arg Ala Ser Leu Ile Asn Asn Ala Phe Gln Leu Val Ser Ile Gly Lys
                 630
                                    635
Leu Ser Ile Glu Lys Ala Leu Asp Leu Ile Leu Tyr Leu Lys Asn Glu
              645
                                650
Thr Glu Ile Met Pro Ile Phe Gln Gly Leu Asn Glu Leu Ile Pro Met
          660
                   665
Tyr Lys Leu Met Glu Lys Arg Asp Met Val Glu Val Glu Thr Gln Phe
      675
                         680
                                            685
Lys Asp Phe Leu Leu Arg Leu Leu Lys Asp Leu Ile Asn Lys Gln Thr
 690
                   695
                                      700
Trp Thr Asp Glu Gly Ser Val Ser Glu Arg Met Leu Arg Ser Gln Leu 705 710 715 720
Leu Leu Leu Ala Cys Val His Arg Tyr Gln Leu Cys Val Gln Arg Ala 725 730 735
Glu Arg Tyr Phe Arg Glu Trp Lys Ala Ser Asn Gly Asn Met Ser Leu
          740
                             745
                                              750
Pro Ile Asp Val Thr Leu Ala Val Phe Ala Val Gly Ala Gln Asn Thr
       755
                        760
Glu Gly Trp Asp Phe Leu Tyr Ser Lys Tyr Gln Ser Ser Leu Ser Ser
```

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770
                     775
                                      780
Thr Glu Lys Ser Gln Ile Glu Phe Ser Leu Cys Ile Ser Gln Asp Pro
785
              790
                          795
Glu Lys Leu Gln Trp Leu Leu Asp Gln Ser Phe Lys Gly Glu Ile Ile
             805
                              810
Lys Thr Gln Glu Phe Pro His Ile Leu Thr Leu Ile Gly Arg Asn Pro
                  825
         820
Val Gly Tyr Pro Leu Ala Trp Lys Phe Leu Lys Glu Asn Trp Asn Lys
      835
              840
                                        845
Ile Val Gln Lys Phe Glu Leu Gly Ser Ser Ser Ile Ala His Met Val
           855
 850
                               860
Met Gly Thr Thr Asn Gln Phe Ser Thr Arg Ala Arg Leu Glu Glu Val
865
       870
                                  875
Lys Gly Phe Phe Ser Ser Leu Lys Lys Asn Gly Ser Gln Leu Arg Cys
           885 890 895
Val Gln Gln Thr Ile Glu Thr Ile Glu Glu Asn Ile Arg Trp Met Asp
         900
                         905
                                            910
Lys Asn Phe Asp Lys Ile Arg Leu Trp Leu Gln Lys Glu Arg Gln Glu
                       920
Leu Leu
   930
<210> 637
<211> 161
<212> PRT
<213> Rat
<400> 637
Met Ala Tyr His Ser Gly Tyr Gly Val His Ala Met Ala Phe Ile Thr
             5 .
                             10
Tyr Val Leu Leu Ala Gly Met Ala Leu Gly Ile Gln Gln Arg Phe Ser
       20
                           25
                                             30
Pro Glu Val Leu Gly Leu Cys Ala Ser Thr Ala Leu Val Trp Val Leu
     35
                      40
Met Glu Val Leu Ala Leu Leu Leu Gly Leu Tyr Leu Ala Thr Val Arg
50 55
                               60
Ser Glu Leu Gly Thr Phe His Leu Leu Ala Tyr Ser Gly Tyr Lys Tyr 65 70 75 80
Val Gly Met Ile Leu Ser Val Leu Thr Gly Leu Leu Phe Gly Ser Asp
           85
                            90
Gly Tyr Tyr Val Ala Leu Ala Trp Thr Ser Ser Ala Leu Met Tyr Phe
                          105 110
         100
Thr Val Arg Ser Leu Arg Thr Ala Ala Ser Gly Pro Asp Ser Met Gly
     115
                      120
                            125
Gly Pro Thr Pro Arg Gln His Leu Gln Leu Tyr Leu Thr Leu Gly Ala
  130
                   135
                                     140
Ala Ala Phe Gln Pro Leu Ile Ile Tyr Trp Leu Thr Phe His Leu Val
145
                 150
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Arg
<210> 638
<211> 165
<212> PRT
<213> Rat
<400> 638
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Met Ala Arg Ala Ala Gly Ile Thr Ala Ala Ile Thr Leu Ala Leu Leu
                5
                                   10
Gly Val Leu Ala Leu Gly Ala Gly Asp Gly Asp Phe Arg Leu Asp Asp
           20
                               25
                                                  30
Ala Leu Glu Asp Thr Asp Lys Lys Pro Thr Pro Lys Pro Pro Thr Pro
                          40
                                             45
Lys Lys Pro Ser Ser Gly Asp Phe Asp Leu Glu Glu Ala Leu Thr Gly 50 55 . 60
Gly Ala Asp Glu Asp Pro Arg Arg Pro Gly Ser Arg Pro Lys Pro Asp
65
                  70
Pro Lys Pro Pro Gly Pro Pro Arg Asp Ser Gly Gly Ile Ser Asp Arg
             85
                                  90
Asp Leu Glu Asp Val Ala Gly His Gly Gly Arg Gly Gly Gly Ala Gly
          100
                             105
Asp Arg Gly Thr Asp Gly Ala Glu Ser Glu Gly Gln Pro Gln Gly Leu
      115
                        120
                                            125
Ile Pro Gly Val Val Ala Ala Val Leu Ala Ala Leu Ala Gly Ala Val
 130
                    135
                                         140
Ser Ser Phe Val Ala Tyr Gln Lys Arg Arg Leu Cys Phe Arg Glu Gly
                  150
                                      155
Gly Ser Ala Pro Val
<210> 639
<211> 61
<212> PRT
<213> Rat
<400> 639 .
Met His Ile Tyr Lys Tyr Val His Ile Asn Tyr Tyr Leu His Leu His
                                  10
Ile Cys Ile Tyr Val Tyr Thr His Ile Ser Val Gly Met Cys Ile Arg
          20
                               25
                                                  30
Ile Cys Leu Pro Ser Ser Ser His Trp Lys Lys Glu Ser Ile Arg Ser
 35
                          40
Gly Gly Ser Lys Asn Ala His Tyr Pro Gly Ser Gly Ile
 50
                       55
<210> 640
<211> 73
<212> PRT
<213> Rat
<400> 640
Met Cys Phe Ser Leu Cys Ser Val Glu Val Phe Phe Leu Lys Gln Asn
                                  10
                                                <sub>-</sub>. 15
Ser Asn Leu Leu Pro Ala His Ile Phe Ile Arg Ala Ser Pro Ile Cys
        20
                              25
Ile Ile Gly Asn Glu Tyr Glu Tyr Ile Phe Met Tyr Val Cys Asn His
     35
                         40
                                             45
Arg Ser His Leu Tyr Leu Gly Phe Ala Ala Ala Asp Tyr Phe Phe Pro
  50
                    55
                                          60 .
His His Gly Thr Gly Asn Cys Phe Gln
                  70
<210> 641
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<211> 442
<212> PRT
<213> Rat
<400> 641
Met Pro Val Leu Trp Leu Leu Leu Leu Pro Leu Leu Pro Leu Leu 1 5 10 15
Ala Met Leu Cys Gln Gln Arg`Ser Pro Gly Ala Arg Pro Cys Trp Leu
                            25
 20
Ile Ser Leu Gln His Arg Val Ala Cys Val Val Leu Ser Trp Ala Ala
    35
                         40
                                            45
Ala Trp Gln Arg Arg Lys Leu Glu Gln Ser Thr Leu Asn Val Ser Gln
                    55
                                       60
Ser Gln Gln Gln Ala Leu Met Gly Cys Leu Lys Glu Ala Gln Gly Ser
                 70
                                    75
Cys Cys Leu Pro Arg Glu Asn Thr Asp Met Thr Thr Phe Arg Asn Leu
             85
                                90
Pro Leu Thr Lys Thr Ser His Thr Gln Gln Lys Glu Ser Glu Glu Lys
                    105
          100
Leu Leu Pro Pro Thr Leu Pro Gln Tyr His Gly Asp Ala Ser Leu Gln 115 120 125
Val Thr Leu Leu Gly Leu Met Thr Leu Asn Lys Ala Tyr Pro Glu Val
  130
                   135
                                       140
Leu Ala Pro Gly Ser Thr Ala Cys Val Thr Pro Thr Ser Pro Trp Pro
145
           150 .
                                    155
Tyr Ser Val Pro Trp Leu Gly His Ala Leu Gly Arg Val Ser Pro Ile
            165
                               170
Gly Ala Lys Asp Ala Arg Thr Leu Leu Leu Glu Ala Leu Ile Ser Pro
          180
                           185
                                             190
Gly Leu Arg Val Leu Glu Ala Arg Thr Ala Val Glu Leu Leu Asp Val
                        200
                                           205
Phe Val Gly Leu Glu Ala Asp Gly Glu Glu Leu Ala Glu Val Ile Ala
                      215
                                         220
Ser Gly Ser Leu Gly Lys Leu Pro Arg Arg Ala Ala Glu Leu Gln Glu
225 230 230 235 240
          230
                                    235
Ala Leu Glu Gln Gly Pro Arg Gly Leu Ala Leu Arg Leu Trp Pro Lys
245 250 255
              245
                                250
Leu Gln Val Val Val Thr Leu Asp Ala Gly Gly Gln Ala Glu Ala Val
                                               270
          260
                             265
Ala Ala Leu Arg Val Leu Trp Cys Gln Gly Leu Ala Phe Phe Ser Pro
                280
    275
                                           285
Ala Tyr Ala Ala Ser Gly Gly Val Met Ala Ile Asn Leu Trp Pro Glu
290 295 300
                     295
                                        300
Gln Pro Gln Gly Ser Tyr Leu Leu Ser Pro Gly Val Pro Phe Ile Glu
                                   315
               310
Leu Leu Pro Ile Lys Glu Gly Thr Gln Glu Glu Ala Ala Ser Thr Leu 325 330 335
              325
                                330
                                          → 335
Leu Leu Thr Asp Val Arg Arg Glu Glu Lys Tyr Glu Leu Val Leu Thr
          340
                     . 345
Asp Ser Thr Ser Leu Thr Arg Cys Arg Leu Gly Asp Val Val Gln Val 355 360 365
Ile Gly Thr Tyr Asn Gln Cys Pro Val Val Arg Phe Thr Cys Arg Leu
  370
                     375
                                        380.
Gly Gln Thr Leu Ser Val Arg Gly Glu Val Thr Asp Glu Asn Val Phe
                390
                                    395
Ser Val Ala Leu Ala Gln Ala Val Gly Gln Cys Gln Gly Pro Ser Cys
                                . 410
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Pro Pro His Thr Thr Lys Cys Leu Trp Ser
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<213> Rat
<400> 642
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Leu Ser Cys Leu Leu Cys Ser Leu Phe Leu Tyr Ser Val Ser Gly
 20 25
                                 30.
Ser Tyr Ser Arg Cys Pro Val Arg Trp Leu Val Cys Leu Ser Ser Gln
 35
              40 .
                                     45
Leu Pro Trp Ala Thr Ser Gln Ser Leu Leu Lys Arg Lys Leu Ser Met
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Val Val Gln Arg Pro Arg Asn Asp Gly Val Ala Ala Leu Thr Gly Ala
      20
                                         30
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Gly Gly Cys Arg Ala Pro Arg Ala Gly Met Ala Gly Gln Phe Arg Ser
     35
                   40
                                      45
Tyr Val Trp Asp Pro Leu Leu Ile Leu Ser Gln Ile Val Leu Met Gln
          55
                          60
Thr Val Tyr Tyr Gly Ser Leu Gly Leu Trp Leu Ala Leu Val Asp Ala
           70
                              75
Leu Val Arg Ser Asn Pro Ser Leu Asp Gln Met Phe Asp Ala Glu Ile
           85
                            90
Leu Gly Phe Ser Thr Pro Pro Gly Arg Leu Ser Met Met Ser Phe Val
        100
                        105 110
Leu Asn Ala Leu Thr Cys Ala Leu Gly Leu Leu Tyr Phe Ile Arg Arg
     115
                    120
                                      125
Gly Lys Gln Cys Leu Asp Phe Thr Val Thr Val His Phe Phe His Leu
 130 135 140
Leu Gly Cys Trp Leu Tyr Ser Ser Arg Phe Pro Ser Ala Leu Thr Trp
              150
                       155 160
Trp Leu Val Gln Ala Val Cys Ile Ala Leu Met Ala Val Ile Gly Glu
                     170
           165
                                 175
Tyr Leu Cys Met Arg Thr Glu Leu Lys Glu Ile Pro Leu Ser Ser Ala
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Pro Lys Ser Asn Val
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<210> 644
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<212> PRT

<213> Rat <400> 644 Met Pro Ser Leu Leu Ser Leu Val Leu Thr Phe Leu Ala Val Ser Ser Pro Ser Cys Cys Gln Asn Ser Asp Thr Ala Ser Pro Lys Ala Ser Asn Gly Ala Ser Phe Leu Trp Asn Asn Met Arg Leu Pro Glu Tyr Ile Thr Pro Ile His Tyr Asp Leu Met Ile His Ala Asn Leu Ser Thr Leu Thr Phe Trp Gly Lys Thr Glu Val Glu Ile Thr Val Ser Gln Pro Thr Ser Thr Ile Ile Met His Ser His Gln Leu Gln Ile Ser Lys Ala Thr Leu Arg Arg Gly Ala Glu Glu Met Leu Pro Glu Glu Pro Leu Lys Leu Met Glu Tyr Ser Ala His Glu Gln Val Ala Leu Leu Thr Ala Gln Pro Leu Leu Ala Gly Ser Val Tyr Thr Val Ile Ile Thr Tyr Ala Ala Asn Leu 130 135 140 Ser Glu Asn Phe His Gly Phe Tyr Lys Ser Thr Tyr Arg Thr Gln Glu 150 155 Gly Glu Arg Arg Ile Leu Ala Ala Thr Gln Phe Glu Pro Thr Ala Ala Arg Met Ala Phe Pro Cys Phe Asp Glu Pro Ala Leu Lys Ala Ser Phe Ser Ile Lys Ile Lys Arg Asp Pro Arg His Leu Ala Ile Ser Asn Met Pro Leu Val Lys Ser Val Thr Val Ala Glu Gly Leu Ile Glu Asp His Phe Asp Ile Thr Val Lys Met Ser Thr Tyr Leu Val Ala Phe Ile Ile 225 230 230 240 Ser Asp Phe Lys Ser Val Ser Lys Met Thr Lys Ser Gly Val Lys Val Ser Val Tyr Ala Val Pro Asp Lys Ile Asn Gln Ala Asp Tyr Ala Leu Asp Ala Ala Val Thr Leu Leu Glu Phe Tyr Glu Asp Tyr Phe Ser Ile Pro Tyr Pro Leu Pro Lys Gln Asp Leu Ala Ala Ile Pro Asp Phe Gln 290 295 300 Ser Gly Ala Met Glu Asn Trp Gly Leu Thr Thr Tyr Arg Glu Ser Ala 310 315 Leu Leu Tyr Asp Lys Glu Lys Ser Ser Ala Ser Ser Lys Leu Gly Ile Thr Met Thr Val Ser His Glu Leu Ala His Gln Trp Phe Gly Asn Leu 345 350 Val Thr Met Glu Trp Trp Asn Asp Leu Trp Leu Asn Glu Gly Phe Ala Lys Phe Met Glu Phe Val Ser Val Thr Val Thr His Pro Glu Leu Lys 375 , 380 Val Glu Glu Tyr Phe Phe Gly Lys Cys Phe Asn Ala Met Glu Val Asp Ala Leu Asn Ser Ser His Pro Val Ser Thr Pro Val Glu Asn Pro Ala Gln Ile Arg Glu Met Phe Asp Glu Val Ser Tyr Glu Lys Gly Ala Cys

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420
                             425
Ile Leu Asn Met Leu Arg Asp Tyr Leu Ser Ala Asp Thr Phe Lys Arg
                                          445
      435
                        440
Gly Ile Val Gln Tyr Arg Gln Lys Tyr Ser Tyr Lys Asn Thr Lys Asn
  450 . 455
                                      460
Glu Asp Leu Trp Asn Ser Met Met His Ile Cys Pro Thr Asp Gly Thr
465
       470
                                  475
Gln Thr Met Asp Gly Phe Cys Ser Arg Asn Gln His Ser Ser Ser Thr
                        490
           485
Ser His Trp Arg Gln Glu Val Ile Asp Ile Lys Ser Met Met Asn Thr
          500
                           505
                                              510 /
Trp Thr Leu Gln Lys Gly Phe Pro Leu Ile Thr Ile Thr Val Arg Gly
      515
                      520
                                          525
Arg Asn Val His Leu Lys Gln Glu His Tyr Met Lys Gly Ser Glu Cys
535
540
           535
530
                                   540
Phe Pro Glu Thr Gly Ser Leu Trp His Val Pro Leu Thr Phe Ile Thr
                 550
                                555
Ser Lys Ser Asp Ser Val Gln Arg Phe Leu Leu Lys Thr Lys Thr Asp
                       570
           565
Val Ile Ile Leu Pro Glu Ala Val Glu Trp Ile Lys Phe Asn Val Gly
  580
                           585
                                              590
Met Asn Gly Tyr Tyr Ile Val His Tyr Gly Asp Asp Gly Trp Ala Ser
  595
               600
                                          605
Leu Asn Gly Leu Leu Lys Glu Ala His Thr Thr Ile Ser Ser Asn Asp
                    615
                                       620
Arg Ala Ser Leu Ile Asn Asn Ala Phe Gln Leu Val Ser Ile Gly Lys
                630
                                   635
Leu Ser Ile Glu Lys Ala Leu Asp Leu Ile Leu Tyr Leu Lys Asn Glu
             645
                        650
Thr Glu Ile Met Pro Ile Phe Gln Gly Leu Asn Glu Leu Ile Pro Met
          660
                           665
                                              670
Tyr Lys Leu Met Glu Lys Arg Asp Met Val Glu Val Glu Thr Gln Phe 675 . 680 685
Lys Asp Phe Leu Leu Arg Leu Leu Lys Asp Leu Ile Asn Lys Gln Thr 690 695 700
Trp Thr Asp Glu Gly Ser Val Ser Glu Arg Met Leu Arg Ser Gln Leu
                710 · 715 720
Leu Leu Leu Ala Cys Val His Arg Tyr Gln Leu Cys Val Gln Arg Ala
              725
                                730
Glu Arg Tyr Phe Arg Glu Trp Lys Ala Ser Asn Gly Asn Met Ser Leu
         740
                    745
Pro Ile Asp Val Thr Leu Ala Val Phe Ala Val Gly Ala Gln Asn Thr 755 760 765
Glu Gly Trp Asp Phe Leu Tyr Ser Lys Tyr Gln Ser Ser Leu Ser Ser
                                   780
                  775
Thr Glu Lys Ser Gln Ile Glu Phe Ser Leu Cys Ile Ser Gln Asp Pro.
               790
                                 795
Glu Lys Leu Gln Trp Leu Leu Asp Gln Ser Phe Lys Gly Glu Ile Ile
805 810 815
             805
                            810
Lys Thr Gln Glu Phe Pro His Ile Leu Thr Leu Ile Gly Arg Asn Pro
                          825
                                              830
Val Gly Tyr Pro Leu Ala Trp Lys Phe Leu Lys Glu Asn Trp Asn Lys
      835
                        840
                                           845
Ile Val Gln Lys Phe Glu Leu Gly Ser Ser Ser Ile Ala His Met Val
                    855
                              860
Met Gly Thr Thr Asn Gln Phe Ser Thr Lys Ala Arg Leu Glu Lys Val
865
                  870
                             , 875
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Lys Gly Phe Phe Ser Ser Leu Lys Lys Asn Gly Phe Gln Leu Arg Cys
                                890
                                                  895
             885
Val Gln Gln Thr Ile Glu Thr Ile Glu Lys Asn Ile Arg Trp Met Asp
           900
                          905
                                              910
Lys Asn Phe Asp Lys Ile Arg Leu Trp Leu Gln Lys Lys Arg Gln Glu
                         920
                                           925
Leu Leu
 930
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<213> Rat
<400> 645
Met Leu His Asn Val Ser Lys Gly Val Val Tyr Ser Ala Thr Val Val
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Leu Gly Leu Leu Ala Tyr Val Ala Phe Lys Cys Trp Arg Ser Arg Lys
 20
                                            30
                           25
Gln Arg Gln Gln Leu Ala Lys Ala Arg Thr Val Glu Leu Gly Asp Pro
 35
                       40
                                 . 45
Asp Arg Asp Gln Arg His Gly Asp Ser Ser Ile Phe Val Asp Ser Pro
                   55
His Gly Leu Glu Pro Cys Ile Pro Ser Gln Gly Pro His Ala Asp Leu
                 70
                                   75
Gly Cys Arg Leu Tyr Leu His Ile Pro Gln Gln Gln Gln Glu Glu Val
             85
                               90
                                                  95
Gln Arg Leu Leu Ile Leu Gly Glu Pro Ala Lys Gly Trp Gln Gly Leu
          100
                          105
                                              110
Ala Gly Gln Leu Gly Tyr Gln Ala Glu Ala Val Glu Thr Met Ala Cys
                   120 125
      115
Asp Gln Asp Pro Ala Tyr Ala Leu Leu Arg Asp Trp Ala Ala Gln Glu
130 135 140
Gly Ser Gly Ala Thr Leu Arg Val Leu Glu Asp Ala Leu Thr Ala Ile
145 150 155 160
Gly Arg Glu Asp Val Val Gln Val Leu Ser Ser Pro Ala Glu Gly Cys
              165
                           170
Ser Val Val
<210> 646
<211> 298
<212> PRT
<213> Rat
<400> 646
Met Lys Tyr Leu Leu Asp Leu Ile Leu Leu Pro Leu Leu Ile Val
                      10
Phe Cys Ile Glu Ser Phe Ile Lys Arg Leu Ile Pro Lys Lys Lys
         20
                           25
                                              30
Ser Val Ala Gly Glu Ile Val Leu Ile Thr Gly Ala Gly His Gly Ile
   35
                         40
                                          45
Gly Arg Leu Thr Ala Tyr Glu Phe Ala Lys Leu Asn Thr Lys Leu Val
 50
                  55
                                   60
Leu Trp Asp Ile Asn Lys Asn Gly Ile Glu Glu Thr Ala Ala Lys Cys
                  70
                                  75
Arg Lys Leu Gly Ala Gln Val His Pro, Phe Val Val Asp Cys Ser Gln
```

90

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Arg Glu Glu Ile Tyr Ser Ala Val Arg Lys Val Lys Glu Glu Val Gly
         100
                  105
Asp Val Ser Ile Leu Val Asn Asn Ala Gly Val Val Tyr Thr Ala Asp
 115
                120
                                        125
Leu Phe Ala Thr Gln Asp Pro Gln Ile Glu Lys Thr Phe Glu Val Asn
130 135 140
            135
                                     140
Val Leu Ala His Phe Trp Thr Thr Lys Ala Phe Leu Pro Ala Met Met
145 150
                         155
Lys Asn Asn His Gly His Val Val Thr Val Ala Ser Ala Ala Gly His
            165
                            170
                                                175
Thr Val Val Pro Phe Leu Leu Ala Tyr Cys Ser Ser Lys Phe Ala Ala
                          185
         180
                                            190
Val Gly Phe His Arg Ala Leu Thr Asp Glu Leu Ala Ala Leu Gly Cys
195 200 205
                                        205
Thr Gly Val Arg Thr Ser Cys Leu Cys Pro Asn Phe Ile Asn Thr Gly
  210 215 . 220
Phe Ile Lys Asn Pro Ser Thr Asn Leu Gly Pro Thr Leu Glu Pro Glu
         . 230
                                  235
Glu Val Val Glu His Leu Met His Gly Ile Leu Thr Asn Gln Lys Met 245 250 255
                              250
                                        255
Ile Phe Val Pro Gly Ser Ile Ala Leu Leu Thr Val Leu Glu Arg Val
        260
                 265 270
Phe Pro Glu Arg Phe Leu Asp Val Leu Lys His Arg Ile Asn Val Lys
 275
                  280
                                         285
Phe Asp Ala Val Val Gly Tyr Lys Asp Lys
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                     295
<210> 647
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<212> PRT
<213> Rat
<400> 647
Met Asn Ser Val Pro Thr Gln Leu Ile Leu Val Leu Thr Ser Leu Leu
1
                               10
Leu Ile Leu Pro Gly Val Glu Ala Val Glu Ala Gly Asp Ala Ile Ala
. 20
                           25
Leu Leu Gly Val Val Leu Ser Val Thr Gly Ile Cys Ala Cys Leu
 35
                       40
                                          45
Gly Ile Tyr Ala Arg Lys Arg Asn Gly Gln Ile
                     55
  50
<210> 648
<211> 281
<212> PRT
<213> Rat
<400> 648
Val Leu Ser Thr Ala Pro Pro Thr Met Arg Pro Ala Pro Gln Pro Gln
1 5
                  10
Asp Cys Pro Ala Ser Ile Cys Leu Asn Gly Gly Ser Cys Arg Val Gly
         20
                           25
                                           30
Ala Lys His His Leu Glu Cys Leu Cys Pro Glu Gly Phe Ile Gly Leu
                      40
                                        45
Tyr Cys Glu Ser Pro Val Glu Gln Arg Thr Lys Pro Ser Ser Ile Pro
   50
                     55
```

```
Asp Thr Pro Arg Pro Pro Arg Leu Leu Pro Leu Arg Ile Glu Pro Val
             70
65
                                75
Ser Pro Thr Ser Leu Arg Val Glu Leu Gln Arg Tyr Leu Gln Gly Asn
            85 <sup>-</sup>
                      90
                                                95
Thr Val Gln Leu Arg Ser Leu Arg Leu Thr Tyr Arg Asn Leu Ser Gly
        100 105
                                    110
Pro Asp Lys Arg Leu Val Thr Leu Arg Leu Pro Ala Ser Leu Ala Glu
115 120 125
Tyr Thr Val Thr Gln Leu Arg Pro Asn Ala Thr Tyr Ser Ile Cys Val
  130 135 140
Thr Ala Leu Gly Ala Gly Arg Thr Pro Glu Gly Glu Glu Ala Cys Gly 145 150 150 160
             150
Glu Ala Asn Thr Pro Gln Ala Val Arg Ser Asn His Ala Pro Val Thr 165 170 175
Gln Ala Arg Glu Gly Asn Leu Pro Leu Leu Ile Ala Pro Ala Leu Ala
        180 185
                                    190
Ala Val Leu Leu Ala Val Leu Ala Ala Ser Gly Ala Val Tyr Cys Val
     195
               200
                                     205
Arg Arg Ala Arg Ala Ser Ser Thr Ala Gln Asp Lys Gly Gln Val Gly
 210 · 215
                                     220
Pro Gly Thr Gly Pro Leu Glu Leu Glu Gly Val Lys Val Pro Leu Glu
225
       230
                                 235
                                                240
Pro Gly Ser Lys Ala Ser Glu Gly Gly Gly Glu Ala Leu Ser Gly Gly
            245
                             250 255
Pro Glu Cys Glu Val Pro Leu Met Gly Tyr Pro Gly Pro Ser Leu Gln
         260
                  265
Gly Val Leu Pro Ala Gln Pro Tyr Ile
     275
                        280
<210> 649
<211> 88
<212> PRT
<213> Rat
<400> 649
Leu Gly Ser Val Ser Val Thr Thr Ile Glu Pro Cys Val Gln Val Gly
1 5
                              10
Ser Pro Ala Arg His Ser Leu His Pro Pro Leu Cys Ile Ser Ile Gly
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                           25
                                            30
Ala Thr Val Pro Tyr Phe Ala Glu Gly Ser Gly Gly Pro Val Pro Thr
 35
                                        45
                  40
Thr Ser Ala Leu Ile Leu Pro Pro Glu Tyr Ser Ser Trp Gly Tyr Pro
 50
                 55
                                    60
Tyr Glu Ala Pro Pro Ser Tyr Glu Gln Ser Cys Gly Ala Gly Gly Thr
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Asp Val Gly Leu Ile Pro Gly Ser
             85
<210> 650
<211> 290
<212> PRT
<213> Rat
<400> 650
Glu Val Asp Pro Asp Leu Lys Cys Ala Leu Cys His Lys Val Leu Glu
              5
                           10
Asp Pro Leu Thr Thr Pro Cys Gly His Val Phe Cys Ala Gly Cys Val
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Leu Pro Trp Val Val Gln Glu Gly Ser Cys Pro Ser Arg Cys Arg Gly
                         40
     35
                                          45
Arg Leu Ser Ala Lys Glu Leu Asn His Val Leu Pro Leu Lys Arg Leu
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The Leu Lys Leu Asp The Lys Cys Ala His Ala Ala Arg Gly Cys Gly 65 70 75 80
Arg Val Val Lys Leu Gln Asp Leu Pro Glu His Leu Glu Arg Cys Asp 85 90 95
Phe Ala Pro Ala Arg Cys Arg His Ala Gly Cys Gly Gln Leu Leu
                          105
                                             110
         100
Arg Arg Asp Val Glu Ala His Met Arg Asp Ala Cys Asp Ala Arg Pro
                    120
                                         125
      115
Val Gly Arg Cys Gln Glu Gly Cys Gly Leu Pro Leu Thr His Gly Glu
130 135 140
Gln Arg Ala Gly Gly His Cys Cys Ala Arg Ala Leu Arg Ala His Asn
145 150
                            155
Gly Ala Leu Gln Ala Arg Leu Gly Ala Leu His Lys Ala Leu Lys Lys
             165
                                170
Glu Ala Leu Arg Ala Gly Lys Arg Glu Lys Ser Leu Val Ala Gln Leu
                    185
          180
Ala Ala Gln Leu Glu Leu Gln Met Thr Ala Leu Arg Tyr Gln Lys
195 200 205
Lys Phe Thr Glu Tyr Ser Ala Arg Leu Asp Ser Leu Ser Arg Cys Val
                    215
                                        220
Ala Ala Pro Pro Gly Gly Lys Gly Glu Glu Thr Lys Ser Val Thr Leu
              230
                              235
Val Leu His Arg Asp Ser Gly Ser Leu Gly Phe Asn Ile Ile Gly Gly 245 250 255
Arg Pro Cys Val Asp Asn Gln Asp Gly Ser Ser Ser Glu Gly Ile Phe
        260
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                                              270
Val Ser Lys Ile Val Asp Ser Gly Pro Ala Ala Lys Lys Arg Pro Ala
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Asn Ser
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<210> 651
<211> 202
<212> PRT
<213> Rat
<400> 651
Met Ala Arg Pro Arg Pro Arg Glu Tyr Lys Ala Gly Asp Leu Val Phe
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Ala Lys Met Lys Gly Tyr Pro His Trp Pro Ala Arg Ile Asp Glu Leu
                                               30
          20
                             25
Pro Glu Gly Ala Val Lys Pro Pro Ala Asn Lys Tyr Pro Ile Phe Phe
      35
                        40
                                           45
Phe Gly Thr His Glu Thr Ala Phe Leu Gly Pro Lys Asp Leu Phe Pro 50 55 60
Tyr Lys Glu Tyr Lys Asp Lys Phe Gly Lys Ser Asn Lys Arg Lys Gly
                                    75
                 70
Phe Asn Glu Gly Leu Trp Glu Ile Glu Asn Asn Pro Gly Val Lys Phe
              85
                                 90
Thr Gly Tyr Gln Thr Ile Gln Gln Gln Ser Ser Ser Glu Thr Glu Gly
                                                110
           100
                             105
Glu Gly Gly Asn Thr Ala Asp Ala Ser Ser Glu Glu Glu Gly Asp Arg
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```
120
Val Glu Asp Gly Lys Gly Lys Arg Lys Asn Glu Lys Gly Gly Ser Lys
                    135
 130
                              140
Arg Lys Lys Ser Tyr Thr Ser Lys Lys Ser Ser Lys Gln Ser Arg Lys
                           155
               150
Ser Pro Gly Asp Glu Asp Asp Lys Asp Cys Lys Glu Glu Glu Asn Lys
165 170 175
                                       175
Ser Ser Ser Glu Gly Gly Asp Ala Gly Asn Asp Thr Arg Asn Thr Thr
 180
                          185
Ser Asp Leu Gln Lys Ala Gly Glu Gly Thr
                         200
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<210> 652
<211> 79
<212> PRT
<213> Rat
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Met Pro Val Ala Val Gly Pro Tyr Gly Gln Ser Gln Pro Ser Cys Phe
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Asp Arg Val Lys Met Gly Phe Val Met Gly Cys Ala Val Gly Met Ala
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Ala Gly Ala Leu Phe Gly Thr Phe Ser Cys Leu Arg Ile Gly Met Arg
     35
                       40 .
Gly Arg Glu Leu Met Gly Gly Ile Gly Lys Thr Met Met Gln Ser Gly
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                    55
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Gly Thr Phe Gly Thr Phe Met Ala Ile Gly Met Gly Ile Arg Cys
                 70
<210> 653
<211> 555
<212> PRT
<213> Rat
<400> 653
Met Pro Val Asn Leu Gly Gln Ala Leu Gly Leu Leu Pro Phe Leu Ala
1 5
                      10
Lys Ala Glu Asp Ala Thr Phe Ser Gly Ser Asp Val Ile Gln Gln Arg
         20
                                             30
                            25
Glu Leu Ala Asn Pro Glu Thr Ala Arg Gln Leu Phe Arg Gln Phe Arg
    35
                   40
                                     45
Tyr Gln Val Met Ser Gly Pro Gln Glu Thr Leu Arg Gln Leu Arg Lys
           55
                                      60
Leu Cys Phe Gln Trp Leu Arg Pro Glu Val His Thr Lys Glu Gln Ile
                70
Leu Glu Ile Leu Met Leu Glu Gln Phe Leu Thr Ile Leu Pro Gly Glu
             85
                              90
                                         - ب 95
Ile Gln Met Trp Val Arg Lys.Gln Cys Pro Gly Ser Gly Glu Glu Ala 100 105 110
Val Thr Leu Val Glu Ser Leu Lys Gly Asp Pro Gln Lys Leu Trp Gln 115 120 125
                       120
Trp Ile Ser Ile Gln Val Leu Gly Gln Glu Ile Pro Phe Glu Lys Glu
  130
                 135
                                      140 -
Asn Ser Ala Arg Cys Arg Gly Asp Lys Val Glu Pro Ala Leu Glu Ala
                150
                              155 160
Glu Pro Thr Val Glu Val Val Pro Gln Asp Leu Pro Leu Gln Asn Thr
                              , 170
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Ser Ser Ala Pro Gly Glu Leu Leu Ser His Gly Val Lys Glu Glu Ser
         180
                            185
                                               190
Asp Met Glu Pro Glu Leu Ala Leu Ala Ala Ser Gln Leu Pro Ala Arg
      195
                         200
                                          205
Ser Glu Glu Arg Pro Thr Arg Asp Gln Glu Val Gly Thr Ala Leu Leu
                    215
 210
                                      220
Pro Ser Leu Gln Glu Gln Gln Trp Arg His Leu Asp Ser Thr Gln Lys
                 230
                                   235
Glu Gln Tyr Trp Asp Leu Met Leu Glu Thr Tyr Gly Lys Met Val Ser
             245
                               250
Gly Ala Gly Ile Ser Asn Ser Lys Pro Asp Leu Thr Asn Met Ala Glu
          260
                   265
                                              270
Tyr Gly Glu Glu Leu Val Gly Leu His Leu His Ser Ala Glu Lys Met 275 280 285
Ala Arg Ala Pro Cys Lys Glu Asp Arg Gln Glu Asn Asp Lys Glu Asn
 290 . 295
                                       300
Leu Asn Leu Glu Asn His Arg Asp Gln Gly Cys Leu Asp Val Phe Asp
305 310
                                    315
Gln Ala Pro Gly Glu Ala Pro Pro Gln Thr Ala Leu Ser Asp Phe Phe
            325
                              330 335
Gly Glu Ser Glu Pro His His Phe Gly Gly Glu Ser Val Pro Glu Ala
        340
                                            350
                           345
Leu Glu Asn Leu Gln Gly Glu Gly Thr Gly Ala His Leu Phe Pro His
                        360
                                          365
Glu Arg Gly Ser Gly Lys Gln Leu Gly Gln His Ile Gln Ser Ser Ser
                     375
                                        380
Ser Gly Glu Leu Ser Ala Leu Trp Leu Glu Glu Lys Arg Glu Ala Ser
         . 390
                                   395
Gln Lys Gly Gln Ala Arg Ala Pro Met Ala Gln Lys Leu Pro Thr Cys
            . 405
                      410
                                                   415
Arg Glu Cys Gly Lys Thr Phe Tyr Arg Asn Ser Gln Leu Val Phe His
                           425
          420
                                       430
Gln Arg Thr His Thr Gly Glu Thr Tyr Phe His Cys Arg Ile Cys Lys
      435
                       440
                                          445
Lys Ala Phe Leu Arg Ser Ser Asp Phe Val Lys His Gln Arg Thr His
450 455 460
                 455
Thr Gly Glu Lys Pro Cys Lys Cys Asp Tyr Cys Gly Lys Gly Phe Ser 465 470 475 480
Asp Phe Ser Gly Leu Arg His His Glu Lys Ile His Thr Gly Glu Lys
485 490 495
Pro Tyr Lys Cys Pro Ile Cys Glu Lys Ser Phe Ile Gln Arg Ser Asn
                          505
                                      510
Phe Asn Arg His Gln Arg Val His Thr Gly Glu Lys Pro Tyr Lys Cys
      515
                      520
                                   525
Thr His Cys Gly Lys Arg Phe Ser Trp Ser Ser Ser Leu Asp Lys His
                    535 540
Gln Arg Ser His Leu Gly Lys Lys Pro Cys Pro
545
                 550
                                    555
<210> 654
<211> 244
<212> PRT
<213> Rat
<400> 654
Leu Ala Tyr Tyr Asn Pro Phe Tyr Phe Leu Ser Ala Ala Ala Pro Gly
               5
                               . 10
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Pro Gly Ala Ala Thr Ser Ala Gly Ala Thr Pro Thr Ala Val Ala Gly
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                             25
Leu Thr Ala Arg Ala Pro His Val Gln Ala Ser Ala Arg Ala Val Pro
      35
                         40
Val Thr Arg Val Gly Ser Ala Ala Pro Ala Arg Thr Ala Ser Asp Thr
                    55
Gly Arg Gln Ala Gly Arg Glu Tyr Val Ile Pro Ser Leu Ala His Arg
                  70
                                    75
Phe Met Ala Glu Met Val Asp Phe Phe Ile Leu Phe Phe Ile Lys Ala
             85
                                90
                                                   95
Thr Ile Val Leu Ser Ile Met His Leu Ser Gly Ile Lys Asp Ile Ser
                   105
          100
                                               110
Lys Phe Ala Met His Tyr Ile Ile Glu Glu Ile Asp Glu Asp Thr Ser 115 120 125
Met Glu Asp Leu Gln Lys Met Met Ile Val Ala Leu Ile Tyr Arg Leu
                    135
                                       140
Leu Val Cys Phe Tyr Glu Ile Ile Cys Ile Trp Gly Ala Gly Gly Ala
                150
                                  155
145
Thr Pro Gly Lys Phe Leu Leu Gly Leu Arg Val Val Thr Cys Asp Thr
            165
                                170
                                                   175
Ser Val Leu Ile Ala Pro Ser Arg Val Leu Val Ile Pro Ser Ser Asn
         180
                             185
                                                190
Val Ser Ile Thr Thr Ser Thr Ile Arg Ala Leu Ile Lys Asn Phe Ser
               200
                                           205
Ile Ala Ser Phe Phe Pro Ala Phe Ile Thr Leu Leu Phe Phe Gln His
            . 215
                                       220
Asn Arg Thr Ala Tyr Asp Ile Val Ala Gly Thr Ile Val Val Lys Arg
                  230
                                     235
Asn Gly Val Arg
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<210> 655

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<212> PRT

<213> Rat

<400> 655

Met Gly Leu Leu Phe Leu Val Leu Leu Ser Pro Leu Ser Cys Val Leu 5 1 10 15 Gly Leu Pro Phe Tyr Asn Gly Phe Tyr Tyr Ser Asn Gly Leu His Gly 20 25 Arg Thr Leu Gly Asn Gly Tyr Gly Glu Gly Leu Phe Asn Gly Val Lys 35 40 Leu Val Val Glu Thr Thr Glu Glu Ser Leu Phe Ser His Gln Gly Ala 55 60 Ser Val Thr Leu Pro Cys His Tyr His Tyr Glu Pro Ala Leu Ala Ser 70 . 75 Pro Arg His Val Arg Ile Lys Trp Trp Lys Leu Ser Glu Asn Gly Thr 85 90 95 Pro Glu Gln Asp Val Leu Val Ala Ile Gly Gln Arg His Arg Ser Phe 100 110 105 Gly Asp Tyr Gln Gly Arg Val Gln Leu Arg Gln Asp Lys Glu Gln Glu 120 115 . 125 Val Ser Leu Glu Leu Arg Asp Leu Arg Leu Glu Asp Ser Gly Arg Tyr 135 140 130 Arg Cys Glu Val Ile Asp Gly Leu Glu Asp Glu Ser Gly Leu Val Glu 155 .

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Leu Glu Leu Arg Gly Val Val Phe Pro Tyr Gln Pro Arg Glu Gly Arg
              165
                                170
                                                 175
Tyr Gln Leu Asn Phe His Glu Ala Gln Gln Val Cys Gln Glu Gln Asp
          180
                            185
Ala Val Val Ala Thr Phe Glu Gln Leu Phe Arg Ala Trp Glu Glu Gly
     195 ' 200
                                          205
Leu Asp Trp Cys Asn Ala Gly Trp Leu Gln Asp Ala Ser Ser Cys Arg 210 215 220
Phe Gly Thr Ser Ser Cys Arg Ile Arg His Glu Ala Cys Arg Arg Pro
        230 235
Leu Trp Cys Gly Asp Pro Arg Val Asn Pro Pro Thr Pro Cys Leu Thr
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                    250
Arg Arg Gln Asn Leu Gln Leu Arg Thr
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<211> 343
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<213> Rat
<400> 656
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Ser Ala Ala Ile Ala Phe His Trp Ser Pro Leu Leu Ala Val Leu Gln
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Arg Ala Leu Ser Leu His Thr Ala His Ala Thr Lys Asp Met Asp Asn
     35
                        40
                                          45
Leu Phe Gln Leu Val Arg Asn Ile Val Pro Ala Leu Thr Ser Lys Lys
  50
                    55
                                      60
His Lys Gly Gln Asp Gly Arg Ile Gly Ile Val Gly Gly Cys Gln Glu
         70
                                  75
Tyr Thr Gly Ala Pro Tyr Phe Ala Gly Ile Ser Ala Leu Lys Val Gly
            . 85
                               90
                                                  95
Ala Asp Leu Thr His Val Phe Cys Ala Arg Glu Ala Ala Pro Val Ile
         100
                                   . 110
                           105
Lys Ser Tyr Ser Pro Glu Leu Ile Val His Pro Val Leu Asp Ser Ser 115 120 125
Asp Ala Val Glu Val Lys Lys Trp Leu Pro Arg Leu His Ala Leu
  130
               135 140
Val Val Gly Pro Gly Leu Gly Arg Asp Asp Leu Leu Leu Asn Asn Val
                 150
                                   155
Arg Gly Ile Leu Glu Ser Thr Lys Ala Arg Asp Ile Pro Val Val Ile
             165
                               170
                                                 175
Asp Ala Asp Gly Leu Trp Leu Ile Ala Gln Arg Pro Ala Leu Val His
         180
                  185
                                              190
Gly Tyr Gln Lys Ala Val Leu Thr Pro Asn His Val Glu Phe Ser Arg
     195
                      200
                                          205.
Leu Trp Asp Ala Val Leu Ser Ser Pro Met Asp Thr Ser Asn His Ser
           215
                               220
Gly Ser Val Leu Lys Leu Ser Gln Ala Leu Gly Asn Ile Thr Ile Val 225 230 235 240
Gln Lys Gly Glu Gln Asp Leu Ile Ser Asn Gly Gln Gln Val Leu Val
             245
                      250
Cys Asn Gln Glu Gly Ser Ser Arg Arg Cys Gly Gly Gln Gly Asp Leu
         260
                           265
                                            270
Leu Ser Gly Ser Leu Gly Val Met Ala His Trp Ala Leu Arg Ala Gly
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280

285

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Pro Glu Lys Thr Asn Gly Ser Ser Pro Leu Leu Val Ala Ala Trp Gly
                     295
   290
Ala Cys Thr Leu Thr Arg Glu Cys Asn His Leu Ala Phe Gln Lys Tyr
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Gly Arg Ser Thr Thr Thr Thr Asp Met Ile Ala Glu Val Gly Ala Ala
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Phe Ser Lys Leu Phe Thr Thr
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Ile Leu Phe Phe Leu Phe Lys Gln Val Ser Val Arg Thr Cys Tyr Leu
    20
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                                              30
Ser Thr Glu Gly Lys Pro Cys Gly Ser Val Leu Phe Ala Cys Lys Ser
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L'eu Gln Gln Cys Leu Leu Thr Val Leu Val Thr Pro Val
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                                                   15
Tyr Ala Gly Asp His Gly Glu Asp Thr Ala Phe Asp Leu Phe Ser Ile
          20
                             25
                                               30
Ser Asn Ile Asn Arg Lys Thr Ile Gly Ala Lys Gln Phe Arg Gly Pro
      35
                         40
                                            45
Asp Pro Gly Val Pro Ala Tyr Arg Phe Val Arg Phe Asp Tyr Val Pro
 . 50
                     55
Pro Val Asn Thr Asp Asp Leu Asn Arg Ile Val Lys Leu Ala Arg Arg
                  70
                                    75
Lys Glu Gly Phe Phe Leu Thr Ala Gln Leu Lys Gln Asp Arg Lys Ser
                                90
                                                   95
              85
Arg Gly Thr Leu Leu Val Leu Glu Gly Pro Gly Thr Ser Gln Arg Gln
          1.00
                   105
                                      . 110
Phe Glu Ile Val Ser Asn Gly Pro Gly Asp Thr Leu Asp Leu Asn Tyr
      115
                         120
                                            125
Trp Val Glu Gly His Gln His Thr Asn Phe Leu Glu Asp. Val Gly Leu
                   135
                                       140
Ala Asp Ser Gln Trp Lys Asn Val Thr Val Gln Val Ala Ser Asp Thr
                  150
                                     155
                                                        160
Tyr Ser Leu Tyr Val Gly Cys Asp Leu Ile Asp Ser Val Thr Leu Glu
              165
                               170
Glu Pro Phe Tyr Glu Gln Leu Glu Ala Asp Lys Ser Arg Met Tyr Val
         180
                      185
                                               190
Ala Lys Gly Ala Ser Arg Glu Ser His Phe Arg Gly Leu Leu Gln Asn
       195
                         200
                                            205
Val His Leu Val Phe Ala Asp Ser Val Glu Asp Ile Leu Ser Lys Lys
```

| | | | | | | | | | | | | | • | | |
|------------|-----|-------------------|-----|------------|------------|-----|------------|------|------------|------------|-----|------------|-----|------------|------------|
| | 210 | | | | | 215 | | | | | 220 | | | | |
| Gly 225 | Cys | Gln | His | Ser | Gln 230 | Gly | Ala | Glu | Val | Asn 235 | Thr | Ile | Ser | Glu | His 240 |
| Thr | Glu | Thr | Leu | His 245 | Leu | Ser | Pro | His | Ile 250 | Thr | Thr | Asp | Leu | Val 255 | Val |
| | | Val | 260 | | | | | 265 | | | | | 270 | | |
| Leu | Ser | Asn 275 | Met | Met | Asn | Glu | Leu 280 | Ser | Gly | Leu | His | Val 285 | Met | Val | Asn |
| | 290 | Ser | _ | | | 295 | | | | | 300 | | | | |
| 305 | | Leu | | | 310 | | | | | 3,15 | | | | | 320 |
| | | Glu | | 325 | | | | | 330 | | | | | 335 | |
| | | Thr | 340 | | | | _ | 345 | | _ | | | 350 | | |
| | | 355 | | | | | 360 | | | | | 365 | | | - |
| | 370 | Сув | | | | 375 | | | | _ | 380 | _ | | _ | _ |
| 385 | | Trp | | | 390 | | | | | 395 | | | | | 400 |
| | | Gln | | 405 | | | | | 410 | | · | | | 415 | |
| _ | | Ser | 420 | | | _ | | 425 | • | | _ | _ | 430 | _ | |
| | | Arg 435 | | | | | 440 | | | | | 445 | | | |
| - | 450 | Val | | | - | 455 | _ | | | | 460 | | _ | | - • |
| 465 | | Pro | | | 470 | | | | | 475 | | | | | 480 |
| | | Thr | | 485 | | | | | 490 | | | | | 495 | |
| | | Pro | 500 | | | | | 505 | | | | | 510 | | - |
| | | Arg 515 Lys | | | | | 520 | | • | · | | 525 | | | _ |
| - | 530 | Ser | | | | 535 | _ | | | | 540 | | | | |
| 545 | | Lys | | | 550 | | | | | 555 | | | | | 560 |
| | | Val | | 565 | | | | | 570 | | | | | 575 | ٠ |
| | | Ala | 580 | | | | | 585 | | | | - | 590 | | |
| | | 595 Val | | | | | 600 | | | | | 605 | | | |
| | 610 | | | | | 615 | | | | | 620 | | | | |
| 625 | | Lys | | | 630 | • | | | | 635 | • | | | | 640 |
| | | Lys Cys | | 645 | | | | | 650 | | | | | 655 | |
| | | -30 | 660 | -13 | 1113 | ALG | | 665. | C | - A - | Leu | GTĀ | 670 | 1116 | JGI |

```
Asp Pro Met Tyr Lys Cys Glu Cys Gln Thr Gly Tyr Ala Gly Asp Gly
                        680
                                        685
Leu Ile Cys Gly Glu Asp Ser Asp Leu Asp Gly Trp Pro Asn Ser Asn
  690
                    695
                                       700
Leu Val Cys Ala Thr Asn Ala Thr Tyr His Cys Val Lys Asp Asn Cys
705
         710
                                715
Pro Lys Leu Pro Asn Ser Gly Gln Glu Asp Phe Asp Lys Asp Gly Ile
725 730 735
Gly Asp Ala Cys Asp Glu Asp Asp Asp Asp Gly Val Ser Asp Glu
          740 · 745
Lys Asp Asn Cys Pro Leu Leu Phe Asn Pro Arg Gln Leu Asp Tyr Asp
               760 765
      755
Lys Asp Glu Val Gly Asp Arg Cys Asp Asn Cys Pro Tyr Val His Asn 770 780
Gln Ala Gln Ile Asp Thr Asp Asn Asn Gly Glu Gly Asp Ala Cys Ser
        790 795
Val Asp Ile Asp Gly Asp Asp Val Phe Asn Glu Arg Asp Asn Cys Pro
             805
                             810
                                        815
Tyr Val Tyr Asn Thr Asp Gln Arg Asp Thr Asp Gly Asp Gly Val Gly
        820
                  825
                                    830
Asp His Cys Asp Asn Cys Pro Leu Met His Asn Pro Asp Gln Met Asp 835 840 845
Gln Asp Asn Asp Leu Val Gly Asp Gln Cys Asp Asn Asn Glu Asp Ile
           855
Asp Asp Asp Gly His Gln Asn Asn Gln Asp Asn Cys Pro Tyr Ile Ser 865 870 875 885
Asn Ser Asn Gln Ala Asp His Asp Asn Asp Gly Lys Gly Asp Ala Cys
885 890 895
Asp Ser Asp Asp Asp Asn Asp Gly Val Pro Asp Asp Arg Asp Asn Cys 900 905 910
Arg Leu Val Phe Asn Pro Asp Gln Lys Asp Ser Asp Gly Asp Gly Arg
915 920 925
Gly Asp Ile Cys Lys Asp Asp Phe Asp Asn Asp Asn Val Pro Asp Ile
            935 940
Asp Asp Val Cys Pro Glu Asn Asn Ala Ile Thr Glu Thr Asp Phe Arg 945 950 955 960
Asn Phe Gln Met Val Pro Leu Asp Pro Lys Gly Thr Thr Gln Ile Asp
965 970 975
Pro Asn Trp Val Ile Arg His Gln Gly Lys Glu Leu Val Gln Thr Ala
    980
                    985
Asn Ser Asp Pro Gly Ile Ala Val Gly Phe Asp Glu Phe Gly Ser Val
995 1000 1005
Asp Phe Ser Gly Thr Phe Tyr Val Asn Thr Asp Arg Asp Asp Asp Tyr 1010 1015 1020
Ala Gly Phe Val Phe Gly Tyr Gln Ser Ser Ser Arg Phe Tyr Val Val
1025 1030
                        1035 1040
Met Trp Lys Gln Val Thr Gln Thr Tyr Trp Glu Asp Lys Pro Ser Arg
           1045 1050 · 1055
Ala Tyr Gly Tyr Ser Gly Val Ser Leu Lys Val Val Asn Ser Thr Thr 1060 1065 1070
Gly Thr Gly Glu His Leu Arg Asn Ala Leu Trp His Thr Gly Asn Thr
      1075 1080 1085
Glu Gly Gln Val Arg Thr Leu Trp His Asp Pro Lys Asn Ile Gly Trp
  1090
           1095 1100
Lys Asp Tyr Thr Ala Tyr Arg Trp His Leu Ile His Arg Pro Lys Thr 1105 1110 1115 112
Gly Tyr Met Arg Val Leu Val His Glu. Gly Lys Gln Val Met Ala Asp
```

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1125
                               1130
Ser Gly Pro Ile Tyr Asp Gln Thr Tyr Ala Gly Gly Arg Leu Gly Leu
                 1145 1150
       1140
Phe Val Phe Ser Gln Glu Met Val Tyr Phe Ser Asp Leu Lys Tyr Glu
 , 1155 1160
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Cys Arg Asp Ala
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Ser Ser Ala Val Leu Ser Ser Gly Ser Pro Gly Thr Ala Ala Ala Ser
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                            25
Ser Ser Val Val Ser Glu Ser Ala Val Ser Trp Ala Ala Gly Thr Gln
    35
                      40
Ala Val Leu Arg Cys Gln Ser Pro Arg Met Val Trp Thr Gln Asp Arg
                   55
                                    60
Leu His Asp Arg Gln Arg Val Val His Trp Asp Leu Ser Gly Gly Pro
                70
                                  75
Gly Ser Gln Gly Arg Arg Leu Val Asp Met Tyr Ser Ala Gly Glu Gln
                     90
             85
Arg Val Tyr Gln Pro Arg Asp Arg Asp Arg Leu Leu Leu Ser Pro Ser
100 105 110
Ala Phe His Asp Gly Asn Phe Ser Leu Leu Ile Arg Ala Val Glu Arg
     115
                120
                                         125
Gly Asp Glu Gly Val Tyr Thr Cys Asn Leu His His His Tyr Cys His
  130
                   135
                                      140
Leu Tyr Glu Ser Leu Ala Val Arg Leu Glu Val Thr Asp Asp Pro Leu
               150
                                155
Leu Ser Arg Ala Tyr Trp Asp Gly Glu Lys Glu Val Leu Val Val Ala
            165
                            170
                                                 175
Leu Gly Ala Pro Ala Leu Met Thr Cys Val Asn Arg Glu His Leu Trp
        180 185
Thr Asp Arg His Leu Glu Glu Ala Gln Gln Val Val His Trp Asp Arg
 195
              200
                                       205
Gln Leu Pro Gly Val Pro His Asp Arg Ala Asp Arg Leu Leu Asp Leu
210 215 220
Tyr Ala Ser Gly Glu Arg Arg Ala Tyr Gly Pro Pro Phe Leu Arg Asp
225 230 235 · 240
Arg Val Ser Val Asn Thr Asn Ala Phe Ala Arg Gly Asp Phe Ser Leu
             245
                            250
                                         255
Arg Ile Asp Asp Leu Glu Pro Ala Asp Glu Gly Ile Tyr Ser Cys His
         260
                   265
Leu His His His Tyr Cys Gly Leu His Glu Arg Arg Val Phe His Leu
     275
                        280
                                         285
Arg Val Thr Glu Pro Val Phe Glu Pro Pro Ala Arg Ala Ser Pro Gly
                   295
                                     300
Asn Gly Ser Gly His Asn Ser Val Pro Ser Pro Asp Pro Thr Met Ala
               310
                               315
Arg Gly His Ser Ile Ile Asn Val Ile Val Pro Glu Asp His Thr His
325 330 335
Phe Phe Gln Gln Leu Gly Tyr Val Leu Ala Thr Leu Leu Leu Phe Ile
```

```
340
                          345
Leu Leu Leu Ile Thr Val Val Leu Ala Thr Arg His Arg His Ser Gly
                360 365
 355
Gly Cys Lys Thr Ser Asp Arg Lys Ala Gly Lys Ser Lys Gly Lys Asp
          375
                                   380
Val Asn Met Met Glu Phe Ala Ile Ala Thr Arg Asp Gln Ala Pro Tyr
                        395
385
               390
                                         400
Arg Thr Glu Asp Ile Gln Leu Asp Tyr Lys Asn Asn Ile Leu Lys Glu
           405
                     410 . 415
Arg Ala Gly Leu Ala His Ser Pro Leu Pro Ala Lys Asp Val Asp Leu
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                         425
Asp Lys Glu Phe Arg Lys Glu Tyr Cys Lys
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             5
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Ser Ser Thr Ala Arg Ala Arg Pro Pro Asn Ala Ala Ile Asp Arg Arg
  20
                       25
Gln Gly Gln Leu Leu Phe Ser Cys Pro Trp Ser Cys Ile Thr Ser Thr
 35
              40
His Thr Phe Ile Ala Ser Ser Thr Val Leu Pro Gly Lys Val Gln Ala
 50
                55
                              60
Pro Phe Ser Arg Val Leu Gln Leu Val Arg Gly Arg Ala Ser Ser Pro
                            75 80
65
             70
Lys Leu Met Thr Leu Trp Gly Ala Phe Pro Pro Ala Arg Gly Asp Glu
           85
                            90
                                              95
Val Leu Gly Arg Gly Trp Asn Ile Thr Ser Val Pro Leu Pro Ser His
         100
                         105
                                         110
Ser Arg Gln Val Ala Gly Ser Ala Ser His Thr His Thr Leu Gly Ala
      115
                      120
                                        125
Ala Ser Pro Thr Pro Leu Ser Pro Gly Pro Ala Pro Leu Cys Ser Thr
· 130
                   135
Met Leu Pro Gly Gln Gly Thr Gly Pro Thr Leu Pro Ser Ala Gly Thr
145
             150
                                 155
Val Pro Ala Leu Pro Ser Ala Ala Thr Gly Glu Gly Trp Gly Gln Val
165 170 175
Ser Arg Gly Pro His Pro Val Arg Asp Gly Val Val His Ile Pro Trp
        180 185
                                  190
Thr Cys Thr Trp Cys Leu Met Ala Ala Pro Thr Arg Asn Thr Pro Met
                                   205
     195 200
Ser Ser Ile Gly Asn Met Ser His Gly His
 210
                   215
<210> 661
<211> 108
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<213> Rat
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              5
                            , 10
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Asp Leu Glu Tyr Ile Tyr Asn Leu Asp Gly Ile Gln Val Arg Asn Lys
         20
                           25
Ala Ile Gly Cys Pro Gln Arg His Gln Leu Pro Ala Leu Gln Glu Ala
     35
                        40
                                          45
Thr Ala Phe Ala Gly Val His Arg Pro Leu Gln Ile His Pro Leu Gly
                   55
                                    60
Arg Gly Leu Arg Pro Trp Glu Gln Gln Gln Arg His Cys Gly His
                 70
                            75
Ile Trp Pro Gly Trp Glu Pro Leu Arg Ser Asp Ser Leu Ala Leu Gly
             85
                              90
Thr Ala Ser Cys Glu Thr Asn Arg Asn Ser Pro Leu
          100
                            105
<210> 662
<211> 516
<212> PRT
<213> Rat
<400> 662
Asn Gln Gly Arg Arg Gly Arg Ser Ser Lys Pro Ser Ile Lys Thr Pro 1 5 10 15
Glu Pro Ile Val Pro Thr Gly Pro Glu Leu Gln Pro Leu Thr Ser Ala
 . 20
                         25
Glu Gln Pro Val Thr Pro Asn Leu Thr Ser Arg Ala Ser Arg Gly Arg
  35
                       40
                                          45
Ser Asn Lys Ser Ile Arg Thr Pro Glu Pro Val Val Gln Thr Gly Pro
          55
                                  60
Glu Phe His Pro Ser Thr Ser Ser Glu Gln Ser Asp Thr Pro Glu Pro
          70
                                75
Ser Ser Gln Gly Arg Thr Arg Arg Ser Val Arg Thr Pro Glu Ala Ser
            85
                            90
Val Ser Thr Thr Pro Ala Leu Gln Pro Ser Thr Ser Lys Lys Gln Pro
         100
                            105
                                            110
Thr Pro Lys Pro Thr Ala Leu Val Thr Arg Gly Arg Thr His Lys Pro
     .115
               120
                                         125
Ser Thr Glu Gly Leu Glu Ser Val Gly Pro Val Ala Pro Asp Phe Glu
 130
                    135
                                     140
Pro Pro Thr Ser Thr Asp His Leu Ala Thr Ser Lys Val Thr Gly Gln
145
                                  155
                150
Ser Leu Thr Leu Gln Ser Ser Pro Val Ser Ala Ser Pro Val Ser Thr
           165
                            170
                                                175
Thr Pro Glu Leu Lys Pro Pro Val Pro Ile Ala Gln Pro Leu Thr Leu
         180
                          185
                                     190
Glu Pro Val Pro Gln Thr Ser His Gln Arg Arg Arg Arg Ala Thr Gly
     195 200
                                  205
Lys Gln Gly Ser Arg Thr Ala Pro Val Gly Pro Lys Ser Tyr Ser Thr.
  210
                   215
                                    220 _-
Pro Ala Glu Pro Glu Pro Gln Ser Ser Ala Ser Gln Ser Ser Gly Ala
225
               230
                                 235
Ser Glu Ala Asp Ser Pro His Gln Lys Arg Pro Arg Arg Gln Val Thr $245$ $250$ $255$
Gln Lys Thr Val Val Lys Glu Glu Asp Pro Gly Glu Ile Gln Val
         260
                           265 · 270
Lys Glu Glu Pro Gln Glu Thr Ala Ile Ser Thr Pro Gly Lys Arg Lys
    275
                     280 285
Arg Asp Pro Ala Glu Gly Glu Thr Gln Gly Asn Pro Thr Arg Ser Arg
                     295
                                     300
```

```
Arg Thr Lys Pro Asn Gln Glu Ala Ala Ala Pro Lys Val Leu Phe Thr
        310
305
                     315
Gly Val Val Asp Ser Arg Gly Glu Arg Ala Val Leu Ala Leu Gly Gly
            325
                                              335
                   · 330
Ser Leu Ala Ser Ser Val Asn Glu Ala Ser His Leu Val Thr Asp Arg
        340
                    345
                                   350
Ile Arg Arg Thr Val Lys Phe Leu Cys Ala Val Gly Lys Gly Ile Pro
355 360 365

Ile Leu Ser Leu Asn Trp Leu Tyr Gln Ser Arg Lys Ala Gly Cys Phe
  370 375
                          380
Leu Pro Pro Asp Asp Tyr Leu Val Thr Asp Pro Glu Gln Glu Lys Asn 385 390 395 400
                                395
Phe Ser Phe Ser Leu Arg Asp Ser Leu Ser Arg Ala Arg Glu Arg Arg
       405
                            410
Leu Leu Glu Asp Tyr Glu Ile His Val Thr Pro Gly Val Gln Pro Pro
        420
                       425
Pro Pro Gln Met Gly Glu Ile Ile Ser Cys Cys Gly Gly Thr Val Leu
  435
               440
                                      445
Pro Ser Met Pro His Ser Tyr Lys Leu His Arg Val Val Ile Thr Cys
 450 455
                            460
Thr Glu Asp Leu Pro Arg Cys Ala Ile Ala Ser Arg Leu Gly Leu Pro
      470
                        475
465
Leu Leu Ser Pro Glu Phe Leu Leu Thr Gly Val Leu Lys Gln Glu Ala
    485 490 495
Thr Pro Glu Ala Trp Ser Ser Pro Ile Trp Lys Cys Ser Leu Pro Lys
        500
                   505
Lys Lys Lys Lys
    515
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1
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                         25
Leu Gln Trp Val Pro Gly Ser Asp Gly Ala Ser Pro Ile Arg Tyr Phe
     35
                   40
                                      45
Thr Val Gln Val Arg Glu Leu Pro Gly Gly Glu Trp Gln Thr Tyr Ser
50 55 60
               55 60
  50
Ser Ser Ile Ser His Glu Ala Thr Leu Cys Ala Val Glu Arg Leu Arg
       70 75
65
Pro Phe Thr Ser Tyr Lys Leu Arg Leu Lys Ala Thr Asn Asp Ile Gly
           85
                           90 - 95
Asp Ser Asp Phe Ser Ala Glu Thr Glu Ala Val Thr Thr Leu Gln Asp
        100
                       105 110
Val Pro Gly Glu Pro Pro Gly Ser Val Ser Ala Thr Pro His Thr Thr
     115
                      120
                               125
Ser Ser Val Leu Ile Gln Trp Gln Pro Pro Arg Asp Glu Ser Leu Asn
               135
                        140 ·
Gly Leu Leu Gln Gly Tyr Arg Ile Tyr Tyr Arg Glu Leu Glu Ser Glu
             150
                              155
Thr Gly Leu Ser Pro Glu Pro Lys Thr Leu Lys Ser Pro Ser Ala Leu
            165
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Arg Ala Glu Leu Thr Ala Gln Ser Ser Phe Lys Thr Val Asn Ser Ser Ser Thr Leu Thr Thr Tyr Glu Leu Thr His Leu Lys Lys Tyr Arg Arg Tyr Glu Val Ile Met Thr Ala Tyr Asn Ile Ile Gly Glu Ser Pro Ala Ser Val Pro Val Glu Val Phe Val Gly Glu Ala Ala Pro Ala Met Ala Pro Gln Asn Ile Gln Val Thr Pro Leu Thr Ala Ser Gln Leu Glu Val · 245 Thr Trp Asp Pro Pro Pro Pro Glu Ser Gln Asn Gly Asn Ile Gln Gly Tyr Lys Val Tyr Tyr Trp Glu Ala Asp Ser Arg Asn Glu Thr Glu Lys Met Lys Val Leu Phe Leu Pro Glu Pro Val Val Lys Ile Lys Asp Leu Thr Ser His Thr Lys Tyr Leu Val Ser Ile Ser Ala Phe Asn Ala Ala Gly Asp Gly Pro Arg Ser Asp Pro Cys Gln Gly Arg Thr His Gln Ala Ala Pro Gly Pro Pro Ser Phe Leu Glu Phe Ser Glu Ile Thr Ser Thr 345 · Thr Leu Asn Val Ser Trp Gly Glu Pro Ser Ala Ala Asn Gly Ile Leu Gln Gly Tyr Arg Val Val Tyr Glu Pro Leu Ala Pro Val Gln Gly Val 370 375 380 Ser Lys Val Val Thr Val Asp Val Lys Gly Asn Trp Gln Arg Trp Leu 395 390 395 400 Lys Val Arg Asp Leu Thr Lys Gly Val Thr Tyr Phe Phe Arg Val Gln Ala Arg Thr Ile Ala Tyr Gly Pro Glu Leu Gln Ala Asn Val Thr Ala Gly Pro Ala Glu Gly Ser Pro Gly Ser Pro Arg Asn Val Leu Val Thr Lys Ser Ala Ser Glu Leu Thr Leu Gln Trp Thr Glu Gly Asn Thr Gly Asn Thr Pro Thr Thr Gly Tyr Val Ile Glu Ala Arg Pro Ser Asp Glu Gly Leu Trp Asp Met Phe Ala Lys Asp Ile Pro Arg Ser Ala Thr Ser Tyr Thr Val Gly Leu Asp Lys Leu Arg Gln Gly Val Thr Tyr Glu Phe 500 505 510 Arg Val Val Ala Val Asn Lys Ala Gly Phe Gly Glu Pro Ser Arg Pro Ser Ile Ala Val Ser Ala Gln Ala Glu Ala Pro Phe Tyr Glu Glu Trp Trp Phe Leu Leu Val Ile Ala Leu Ser Ser Leu Leu Leu Val Leu Leu Val Val Phe Val Leu Val Leu His Gly Gln Ser Lys Lys Tyr Lys Asn Cys Gly Ser Gly Lys Gly Ile Ser Asn Met Glu Glu Thr Val Thr Leu Asp Asn Gly Gly Phe Ala Ala Leu Glu Leu Asn Ser Arg His Leu Asn Val Lys Ser Thr Phe Ser Lys Lys Asn Gly Thr Arg Ser Pro Pro Arg Pro Ser Pro Gly Gly Leu His Tyr Ser Asp Glu Asp Ile Cys Asn Lys

630

```
Tyr Asn Gly Ala Val Leu Thr Glu Ser Val Asn Leu Lys Glu Lys Ser
                      650 655
           645
Val Asp Gly Ser Glu Ser Glu Ala Ser Asp Ser Asp Tyr Glu Glu Ala
        660
               665 . 670
Leu Pro Lys His Ser Phe Val Asn His Tyr Met Ser Asp Pro Thr Tyr 675 680 685
675 680 685
Tyr Asn Phe Trp Lys Arg Arg Pro Pro Ala Ala Ala Pro His Arg Tyr
                 695
Glu Ala Val Ala Gly Ala Glu Ala Gly Pro His Leu His Thr Val Ile
705 710 715 720
Thr Thr Gln Ser Ala Gly Gly Val Tyr Thr Pro Ala Gly Pro Gly Ala 725 730 735
Arg Ala Pro Leu Thr Gly Phe Ser Ser Phe Val
          740
                            745
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<211> 307
<212> PRT
<213> Rat
<400> 664
Met Gln Leu Asn Arg Phe Phe Ser Gly Pro Gly Leu Phe Leu Leu
             5
                               10
Phe Cys Ser Leu Cys Val Glu Ala Glu Val Lys Glu Val Asn Ala Met
 . 20 . 25
Val Gly Ser Asp Val Glu Leu Arg Cys Val Tyr Pro Arg Arg Ser His
35 40 45
Phe Ser Leu Asp Asp Leu Tyr Val Tyr Trp Gln Ile Val Asp Glu Ala 50 55 60
Lys Thr Val Val Thr Tyr Tyr Leu Pro Ser Ala Asn Glu Ser Ser Thr
               70
                                75
Ile His Val Ser Asn Ser Tyr Lys Asn Arg Ala His Leu Ser Pro Asp
             85
                            90
Leu Met Lys Glu Gly Asp Phe Ser Leu His Leu Gln Asn Val Thr Pro
. 100 105 110
Gln Asp Thr Gln Glu Phe Lys Cys Leu Val Phe Arg Met Ser Thr Val
115 120 125
Leu Gly Lys Ala Leu Glu Glu Val Val Arg Leu Arg Val Ala Ala Asn
130 135 140
Glu Arg Thr Phe Thr Cys Met Ser Lys Asn Gly Tyr Pro Glu Pro Asn
           165 170
                                                175
Leu Tyr Trp Ile Asn Arg Thr Asp Asn Thr Leu Ile Asp Glu Thr Leu
         180
                           185
                                            190
Gln Asn Asn Thr Val Tyr Leu Asn Glu Leu Gly Leu Tyr Asp Val Val
                    200
                                      205
Ser Thr Leu Arg Ile Pro Trp Thr Pro His Val Asp Val Ile Cys Cys 210 215 220
 210
                    215
                                     220
Val Glu Asn Val Ala Leu His Gln Asn Ile Thr Ser Ile Ser Arg Ala
                230
                                 235
Arg Glu Ala Thr Lys Val Leu Phe Tyr Ala Leu Ala Ala Leu Leu Ala 260 265 270
Val Val Val Ile Phe Ile Ile Val Leu Tyr Arg Cys Arg Arg Arg
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285

280

275

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Asp His Ser
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Thr Val Asn Ala Leu His Pro Gly Val Ala Arg Thr Glu Leu Gly Arg
    35
                        40
                                          45
His Thr Gly Met His Asn Ser Ala Phe Ser Gly Phe Met Leu Gly Pro
          55
 50
                                      60
Phe Phe Trp Leu Leu Phe Lys Ser Pro Gln Leu Ala Ala Gln Pro Ser 65 70 75 80
65
               70
                                 75
Thr Tyr Leu Ala Val Ala Glu Glu Leu Glu Ser Val Ser Gly Lys Tyr
        85 90
Phe Asp Gly Leu Arg Glu Lys Ala Pro Ser Pro Glu Ala Glu Asp Glu
          100
                           105
                                             110
Glu Val Ala Arg Arg Leu Trp Thr Glu Ser Ala His Leu Val Gly Leu
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Asp Met Ala His Gly Ser Ser Gly Arg Gly His Ser Ile Ser Arg
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Val Leu Ala His Leu Glu Arg Leu Glu Ala Gln Thr Asn Ile Ser Asn
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                                              30
Arg Lys Ser Glu Glu Pro Ala Val Arg Lys Lys Glu Ser Ser Leu Arg
     35
                       40
                                        45
Thr Lys Ile Arg Glu Leu Arg Gln Gln Arg Asp Lys Leu Arg Ala Glu
 50
                    55
                                    60
Val Lys Gln Trp Gly Ala Arg Val Lys Glu Pro Pro Ala Lys Glu Asp
65 '
                  70
                                   75 - 80
Pro Ser Arg Thr Val Ile Ser Glu Gln Glu Val Leu Glu Arg Glu Trp
             85
                              90 95
Arg Asn Val Asp Ala Ile Leu Glu Ala Tyr Arg Phe Thr Gly Leu Ser 100 105 110
Gly Lys Leu Thr Ser Arg Gly Val Cys Met Cys Ile Ser Thr Ala Phe
      115
                       120
Glu Gly Asn Leu Leu Asp Ser Tyr Phe Val Asp Leu Val Ile Glu Lys
 130
                135
                            . 140
Pro Leu Arg Ile His His Ser Val Pro Val Phe Ile Pro Leu Glu
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                                   155
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Lys Ile Ala Ala Ala His Leu Gln Thr Asp Val Gln Arg Phe Leu Phe
              165
                               170
Arg Leu Trp Glu Tyr Leu Asn Ala Tyr Ala Gly Arg Lys Tyr Gln Ala
          180
                        185
Asp Gln Leu Glu Ser Asp Phe Cys Asp Val Leu Thr Gly Pro Leu Gln
     195
                      200
                                        205
Arg Asn Ala Leu Cys Asn Leu Leu Ser Phe Thr Tyr Lys Val Glu Gln
210 215 220
                  215
                                     220
Arg Cys Gln Thr Phe Ser Phe Ser Ala Arg Leu Leu Tyr Glu Asp Pro
225 230 235
                                                     240
Thr Ala Ala Leu Pro Thr Asn Val Thr Val Thr Arg Pro Gly Val Glu
            245
                               250
                                                  255
Ala Ser Ser Pro Pro Trp Glu Glu His Arg Ala Ser His Gln Met Leu
         260
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                                     270
Phe Arg Thr Lys Pro Leu His Lys Val Phe Ala Ser Phe Ser Lys Glu 275 280 285
Thr Glu Lys Leu His Leu Asn Leu Val Ser
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Phe Gln Leu Asn Ser Val Asp Ser Ser Leu Leu Phe Thr Ala Gln Ala
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                           25
                                            30
Leu Leu Arg Trp His Asp Gly His Gln Phe Cys Ser Lys Ser Gly Gln
     35
                       40
                                         45
Pro Thr Gln Lys Asn Val Ala Gly Ser Lys Arg Val Cys Pro Ser Ser
 50
                   55
                                       60
Lys Ile Ile Tyr Tyr Pro Gln Met Ala Pro Val Val Ile Thr Leu Val
               70
                                   75
Ser Asp Gly Ala Arg Cys Leu Leu Ala Arg Gln Ser Ser Phe Pro Lys
              85
                               90
Gly Leu Tyr Ser Ala Leu Ala Gly Phe Cys Asp Ile Gly Glu Ser Val
          100
                           105
                                             110
Glu Glu Thr Val His Arg Glu Val Ala Glu Glu Val Gly Leu Glu Val
      115
                      120
                                          125
Glu Asn Ile Gln Tyr Ser Ala Ser Gln His Trp Pro Phe Pro Asn Ser
 130
                  135
                              140
Ser Leu Met Ile Ala Cys His Ala Thr Val Lys Pro Gly His Thr Glu
               150
145
                                  155
Ile Gln Val Asn Leu Lys Glu Leu Glu Ala Ala Ala Trợ Phe Ser Leu
             165
                              170 . . . 175
Asp Glu Val Thr Thr Ala Leu Arg Arg Lys Gly Ser Leu Ala Leu Gln
         180
                          185
                                    190
Pro Ser Glu Ala Ser Pro Leu Leu Pro Pro Lys Leu Ala Ile Ala
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                                         205
His His Leu Ile Lys Lys Trp Val Glu Thr Arg Ser Cys Ser Ser Leu
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Ala Ala
225
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Ala Ile His Val Leu Ser Gly Val Trp Val Ala Tyr Glu Arg Val Gly
          420
                           425
                                            430
Phe Ser Gly Glu Gln Tyr Ile Leu Glu Lys Gly Val Tyr Arg Asn Cys
       435
                        440
                                        445
Asp Asp Trp Gly Ser Gly Asn Cys Ala Leu Gly Ser Leu Gln Pro Val
                   455
                                      460
Val Gln Val Gly Glu Ser Asp Leu His Phe Val Thr Lys Ile Gln Leu
465
                470
                                  475
Phe Ser Gly Pro Asn Phe Leu Gly Asp His Ile Ser Phe Glu Asp Asp
           485
                            490
Gln Ala Ser Leu Pro Ala Ser Phe His Pro Gln Ser Cys Arg Val His
                 505
        500
                                             510
Gly Gly Ser Trp Val Leu Phe Glu Asp Lys Asn Phe Glu Ala Asp Gln
               520
      515
                                        525
His Ile Val Ser Glu Gly Glu Phe Pro Thr Leu Thr Asp Met Gly Cys
 530 535
                                    540
Leu Ala Ser Thr Val Leu Gly Ser Leu Arg Lys Val Pro Leu His Phe
545
               550
                         555
Ser Glu Pro Ser Leu Ser Leu Phe Gly Leu Glu Cys Phe Glu Gly Lys
                      . 570
            565
                                               575
Glu Ile Glu Leu Thr Gly Glu Val Arg Ser Leu Gln Ala Glu Gly Phe
          580
                        585
                                             590
Asn Asn His Val Leu Ser Val Arg Val Lys Gly Gly Val Trp Val Val
      595
                     600
                                       605
Cys Glu His Ser Asp Phe Arg Gly Arg Gln Trp Leu Val Gly Ser Cys
  610
           615
                                      620
Glu Ile Thr Asn Trp Leu Thr Tyr Ser Gly Thr Gln Arg Val Gly Ser 625 630 635 640
Leu Tyr Pro Ile Lys Gln Arg Arg Ala Tyr Phe Arg Leu Trp Asn Ala
            645
                              650
Ala Leu Gly Gly Phe Leu Ser Val Pro Asp His Val Glu Asp Met Lys
         660
                  665
                                          670
Ala Gly Arg Val Val Ser Glu Pro Arg Ala Gly Gly Ser Cys Ile
               680
      675
                                         685
Trp Tyr Tyr Glu Asp Gly Leu Leu Lys Asn Gln Met Ala Pro Thr Met 690 695 700
Ser Leu Gln Val Ile Gly Pro Pro Ser Pro Gly Ser Lys Val Val Leu
              710 715
Trp Ala Glu Ser Arg Leu Pro Arg Gln Thr Trp Ser Ile Asn Glu Leu
          · 725
                              730
                                          735
Gly His Ile Cys Ser Gln Met Phe Glu Gly Gln Ile Leu Asp Val Lys
         740
              745
Gly Gly Arg Gly Tyr Asp Arg Asp His Val Val Leu Trp Glu Pro Thr 755 760 765
Lys Asp Arg Leu Ser Gln Ile Trp Thr Val His Val Leu
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Met Tyr Met Thr Met Arg Gly Lys Glu Pro Trp Gln Thr Ala Lys Leu
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Gln Leu Gly Glu Leu Asn Arg Thr Ala Val Phe Thr Cys Arg Pro Ala
                           25,
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Arg Val Lys Glu Gly Asp Ile Leu Tyr Ile His Ser Leu Gln Thr Val
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                       40
                                         45
Gly Ser Asn His Lys Pro Val Ala Ala Glu His Thr Tyr Trp Ala Trp
  50
Pro Glu Glu Thr Asp Val
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Asp Thr Ala Asp Pro Gln Glu Asn Pro Leu Gln Pro Val Ser Val Gly
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                           25
Glu Glu Pro Ser Ile Thr Glu His His Ser Val Gly Glu Gln Ala Trp
      35
                      40
Asp Gly Thr Ser Gln Ser Cys Pro Ser Leu Pro Ala Thr Val Ser Phe 50 55 60
           55
His Met Asp Ser Thr Asp Leu Glu Pro Gly Gln Gln Thr Ala Met Lys
              7.0
65
                     75
Ser Cys Ser Arg Asp Asp Val Glu Met Val Glu Glu Phe Asp Glu Leu
             85 90
                                                 95
Pro Thr Asp Ala Val Arg Arg Ile Arg Arg Glu Leu Val Thr Val Thr
                          105
         100
                                            110
Lys His Ser Pro Glu Gln Arg Gln Asp Pro Leu Cys Ile Ser Ile Thr
               120
    115
                                         125
Val Cys Thr Val Glu Lys Asp Arg Pro Ala Ala Leu Asp Ser Leu Glu
                   135
                              140
Glu Pro Leu Pro Gly Met Leu Phe Phe Leu Ser Ser Gly Gln Asp Gln
                 150
                                  155
Gln Ala His Pro Gln Leu Arg Glu His Pro Ala Pro Glu Ala Ser Glu
          165
                   170
                                        175
Ala Ser Gln Pro Gln Asp Ala Ala Glu Glu Ser Ser Ala Gly Glu Glu
180 185 · 190
                                    · 190
          180
                          185
Lys Asp Ala Ser Val Glu Pro Leu Leu Pro Ala Ala Ser Pro Gly Gly
      195
                        200
                                         205
Ser Thr Ser Gln Val Leu Glu Ala Ala Thr Cys Lys Lys Gln Val Ser
 210
                                     220
                   215
Gln Asp Phe Leu Glu Thr Arg Phe Lys Ile Gln Gln Leu Leu Glu Pro
225
                230
                                   235
Gln Gln Tyr Met Ala Cys Leu Pro His His Ile Ile Val Lys Ile Phe
            245
                              250
Arg Leu Leu Pro Thr Leu Ser Leu Ala Ile Leu Lys Cys Thr Cys Arg
          260
                          265
                                            . .270
Tyr Phe Lys Ser Ile Ile Glu Tyr Tyr Asn Ile Arg Pro Ala Asp Ser
                       280
     275
Arg Trp Val Arg Asp Pro Arg Tyr Arg Glu Asp Pro Cys Lys Gln Cys 290 295 300
   290
           295
                                      300
Lys Lys Lys Tyr Val Lys Gly Asp Val Ser Leu Cys Arg Trp His Pro
             310
                                  315
Lys Pro Tyr Cys Gln Ala Leu Pro Tyr Gly Pro Gly Tyr Trp Met Cys
            · 325
                                                335
                              330
Cys Pro Pro Val Ser Glu Gly Leu Phe Cys Cys Lys Leu Gly Leu His
          340
                            345
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Asp Asn His Trp Leu Pro Ala Cys His Ser Phe Asn Pro Gly Asn Pro
                        360
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Glu Ser Leu Gly Asp Leu Glu Ser Pro Val Glu Asp Thr Pro Val Glu
                       25
       20
Gln Ala Ala Leu Ser Pro Phe Pro Pro Ser Lys Pro Pro Val Ser Ser
     35 . 40
Glu Leu Gly Asp Ser Ser Cys Ser Ser Asp Met Thr Asp Ser Ser Thr
  50 55
                                   60
Thr Leu Ser Ser Gly Ser Ser Glu Pro Pro Asn His Pro Ala His Pro 65 70 75 80
Ser Leu Pro Gly Pro Ser Phe Arg Ser Gly Val Asp Glu Asp Ser Leu
85 90 95
Glu Gln Ile Leu Asn Phe Ser Asp Ser Asp Leu Gly Ile Glu Glu
        100
                        105
                                          110
Glu Glu Glu Gly Gly Val Gly Asn Ser Asp Asn Leu Ser Cys Phe
    115
                      120
                              125
His Leu Ala Asp Ile Phe Gly Thr Gly Asp Pro Gly Ser Leu Ala Ser
 130
        135 140
Trp Thr His Ser Gln Ser Gly Ser Ser Leu Ala Ser Gly Ile Leu Asp
145 150 150 155 160
                        155
                150
                                                 160
Glu Asn Ala Asn Leu Asp Ala Ser Cys Phe Leu Asn Ser Gly Leu Gly
            165
                             170
                                              175
Gly Leu Arg Glu Gly Ser Leu Pro Gly Ser Ser Gly Ser Pro Glu Gly
         180
                         185
Asp Ala Val Gin Ser Ser Ser Trp Asp Leu Ser Leu Ser Ser Cys Asp 195 200 205
Ser Phe Glu Leu Leu Gln Ala Leu Pro Asp Tyr Ser Leu Gly Pro His
 210 215 220
Tyr Thr Ser Arg Arg Val Ser Gly Ser Pro Asp Ser Leu Glu Thr Phe
225 230 235
His Pro Leu Pro Ser Phe Ser Pro Pro Arg Asp Ala Ser Thr Cys Phe
          245 250 255
Leu Glu Ser Leu Val Gly Leu Ser Glu Pro Val Thr Glu Val Leu Ala
                  265
         260
                                          270 .
Pro Leu Leu Glu Ser Gln Phe Glu Asp Ala Ala Leu Ala Pro Leu Leu
     275
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Glu Pro Val Pro Val
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<400> 672
Met Glu Val Asn Cys Leu Thr Leu Lys Asp Leu Ile Ser Pro Arg Gln
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Thr Arg Leu Asp Phe Ala Ile Glu Asp Ala Glu Asn Ala Gln Lys Glu
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20
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Asn Ile Phe Val Asp Arg Ser Arg Met Thr Pro Lys Thr Pro Met Lys
       35
                         40
Asn Glu Pro Ile Asp Leu Ser Lys Gln Arg Ile Phe Thr Pro Asp Arg
 50
                     55
Asn Pro Ile Thr Pro Val Lys Pro Val Asp Arg Gln Pro Gln Val Glu
65 70 75 80
Pro Trp Thr Pro Thr Ala Asn'Leu Lys Met Leu Ile Ser Ala Ala Ser
           85
                               90
Pro Asp Ile Arg Asp Arg Glu Lys Lys Lys Glu Leu Phe Arg Pro Ile
         100
                            105
                                              110
Glu Asn Lys Glu Asp Ala Phe Val Asn Ser Leu Gln Leu Asp Val Ala
      115
                       120
                                          125
Gly Asp Gly Ala Val Asp Glu Tyr Glu Lys Gln Arg Pro Ser Arg Lys
130 135 140
Gln Lys Ser Leu Gly Leu Leu Cys Gln Lys Phe Leu Ala Arg Tyr Pro
       150
                                  155
Ser Tyr Pro Leu Ser Thr Glu Lys Thr Thr Ile Ser Leu Asp Glu Val
            165
                             170
                                                  175
Ala Val Ser Leu Gly Val Glu Arg Arg Arg Ile Tyr Asp Ile Val Asn
                            185
         180
                                              190
Val Leu Glu Ser Leu His Leu Val Ser Arg Val Ala Lys Asn Gln Tyr
   195 200
                                        205
Gly Trp His Gly Arg His Ser Leu Pro Lys Thr Leu Arg Thr Leu Gln
  210
                     215
                                       220
Arg Leu Gly Glu Glu Gln Lys Tyr Glu Glu Gln Met Ala Cys Leu Gln
               230
                            235
Gln Lys Glu Leu Asp Leu Met Gly Tyr Arg Phe Gly Glu Arg Arg Lys
245 250 255
Asp Gly Ser Pro Asp Pro Arg Asp Pro His Leu Leu Asp Phe Ser Glu
         260
                  265 270
Ala Asp Tyr Pro Ser Ser Ala Asn Ser Arg Lys Asp Lys Ser Leu
                280
      275
                                          285
Arg Ile Met Ser Gln Lys Phe Val Met Leu Phe Leu Val Ser Lys Thr
290 295 300
Lys Ile Val Thr Leu Asp Val Ala Ala Lys Ile Leu Ile Glu Glu Ser
305 310 315
Gln Asp Thr Pro Asp His Ser Lys Phe Lys Thr Lys Val Arg Arg Leu
             325
                               330
                                                   335
Tyr Asp Ile Ala Asn Val Leu Thr Ser Leu Ala Leu Ile Lys Lys Val
         340
                   345
                                      350
His Val Thr Glu Glu Arg Gly Arg Lys Pro Ala Phe Lys Trp Ile Gly
355 360 365
       355
                         360
                                          365
Pro Val Asp Phe Ser Ser Ile Asp Glu Glu Leu Leu Asp Val Ser Ala
  370
                                       380
                     375
Ser Ile Leu Pro Glu Leu Lys Lys Glu Ala Tyr Gly Gln Ile Arg Vaļ
                 390
                                   395
Cys Ala Lys Glu Arg Leu Val Arg Tyr Gly Ser Phe Asn Thr Val His 405 410 415
             405
                                410
Thr Ser Glu Lys Ile Gln Arg Lys Val Ser Ser Glu Pro Ser Ser Pro
         420
                           425
                                            430
Gln Gly Glu Arg Gln Gly Ser Ala Tyr Ser Leu Glu Ile Gly Ser Leu
      435
                         440
                                 . 445
Ala Ala Ile Tyr Arg Gln Lys Val Glu Asp Asn Ser Gln Glu Glu Ala
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                                   460
Phe Val Ser Asn Thr Ala Val Pro Pro Ala Ser Ile Leu Asp Pro Ala
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                  470
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Leu Ser Met Asp Ser Glu Tyr Cys Val Lys Pro Leu Ala Gln Pro Val
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               485
Phe Ser Val Ala Gln Thr Asp Leu Pro Ala Phe Ser Ala Gln Asn Gly
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                            505
                                                510
Pro Ser Gly Gln Val Gly Val Pro Val Pro Ser Ala Ala Ser Asp Thr
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Glu Asn Leu Lys Pro Ala Leu Leu Ala Gly Gln Pro Leu Val Tyr Val
                     535`
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Pro Ser Thr Gln Leu Phe Met Leu Tyr Gly Ser Val Gln Glu Gly Leu
               550
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Ser Pro Glu Ser Arg Ser Glu Glu Asp Gly Gly Gly Ser Asp Val Pro
565 570 575
Ala Asp Leu Ser Val Thr Pro Ser Ala Gln Lys Arg Leu Cys Glu Glu
         580
                    585
                                             590
Arg Asp Pro Gln Glu Glu Glu Asp Glu Pro Ala Met Lys Arg Gln Ser
                       600
      595
                                            605
Gln Glu Phe Glu Asp Ser Pro Leu Ser Leu Val Met Pro Lys Lys Pro
                    615
 610
                                        620
Ser Ser Ser Thr Asp Leu Ala Cys Pro Val Thr Met Gly Asn Gly Ser
                  630
                                  635
                                                        640
Ser Pro Pro Leu Glu Asp Ala Cys Val Lys Gly Gln Leu Pro Ala Ala
             645
                               650
                                                   655
Glu Glu Val Thr Gly Lys Ala Ala Pro Asn Cys Tyr Val Ala Ser Glu
           660
                             665
Cys Gly Asn Pro Ala Arg Asn Pro Asp Thr Glu Lys Pro Ser Asn Glu
      675
                         680
                                           685
Asn Glu Ile Thr Lys Asp Pro Ser Leu Met Gln Tyr Leu Tyr Val Gln
  690
                     695
                                         700
Ser Pro Ala Gly Leu Asn Gly Phe Asn Met Val Leu Pro Gly Thr Gln
705
                 710
                         ... 715
Thr Pro His Thr Val Ala Pro Ser Pro Ala Gln Leu Pro Ser Phe Gly
            725
                               730 -
                                                    735
Val Pro Cys Met Phe Leu Gln Ser Pro Gly Leu Gly Pro Phe Pro Val
          740
                    745
                                             750
Leu Tyr Ser Pro Ala Ile Pro Gly Pro Ile Ser Ser Ala Pro Gly Thr
     755
                760
                                  765
His Pro Asn Pro Gly Pro Met Asn Phe Gly Leu Ser Thr Leu Ala Ser
                      775
                                        780
Ala Ser His Leu Leu Ile Ser Pro Ala Ala Met Val Asn Pro Lys Pro
                 790
                                    795
Ser Thr Leu Pro Cys Thr Asp Pro Gln Leu Arg Cys Gln Pro Ser Leu
805 810 815
Asn Leu Asn Pro Val Met Pro Gly Ser His Gly Val Ile His Pro Glu
          820
                             825
                                                830
Ser Pro Cys Tyr Val Arg His Pro Val Ser Met Val Lys Ala Glu Gln 835 840 845 .
Ser Pro Ala Pro Ala Thr Pro Lys Ser Ile Gln Arg Arg His Arg Glu
850 855 860
Thr Phe Phe Lys Thr Pro Gly Ser Leu Gly Asp Pro Val Phe Arg Arg
                870
                                    875
Lys Glu Arg Asn Gln Ser Arg Asn Thr Ser Ser Ala Gln Arg Arg Leu
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                                  890
Glu Ile Ser Ser Ser Gly Pro Asp
           900
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Glu Val Val Leu Lys Glu Ile Arg Thr Leu Val Asp Met Ala Leu Thr

Ser Pro Leu Gln Asp Asp Ser Ile Asn Gln Ala Pro Leu Glu Ile Val

185 .

165

180

170 175

Ser Lys Leu Leu Ser Glu Asn Thr Asn Leu Thr Thr Gln Glu His Glu
195 200 205

```
Asn Ile Ile Val Ala Ile Ala Pro Leu Leu Glu Asn Asn His Pro Pro
  210
                     215
                                       220
Pro Asp Leu Cys Glu Phe Phe Cys Lys His Cys Arg Glu Arg Pro Arg
                 230
                                  235
Ser Met Val Val Ile Glu Val Phe Thr Pro Val Val Gln Arg Ile Leu 245 250 255
Lys His Asn Met Asp Phe Gly Lys Cys Pro Arg Leu Arg Leu Phe Thr
                 265
       260
                                              270
Gln Glu Tyr Ile Leu Ala Leu Asn Glu Leu Asn Ala Gly Met Glu Val
              280
                                 285
  275
Val Lys Lys Phe Ile Gln Ser Met His Gly Pro Thr Gly His Cys Pro
290 295 300
His Pro Arg Val Leu Pro Asn Leu Val Ala Val Cys Leu Ala Ala Ile
305 310
                                 315
Tyr Ser Cys Tyr Glu Glu Phe Ile Asn Ser Arg Asp Asn Ser Pro Ser
             325
                               330
Leu Lys Glu Ile Arg Asn Gly Cys Gln Gln Pro Cys Asp Arg Lys Pro
        340
                           345
Thr Leu Pro Leu Arg Leu Leu His Pro Ser Pro Asp Leu Val Ser Gln
      355
                       360
                                          365
Glu Ala Thr Leu Ser Glu Pro Arg Leu Lys Ser Val Val Val Ala Ser
                    375
                           380
Ser Glu Val His Val Glu Val Glu Arg Thr Ser Thr Ala Lys Pro Ala
                 390
                                 395
Leu Thr Ala Ser Thr Gly Asn Asp Ser Glu Pro Asn Leu Ile Asp Cys 405 410 415
Leu Met Val Ser Pro Ala Cys Gly Thr Met Ser Ile Glu Leu Gly Pro
        420 425
Gln Ala Gly Arg Thr Leu Gly Cys His Val Glu Ile Leu Lys Leu Leu
    435 ... 440
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Ser Asp Tyr Asp Asp Trp Arg Pro Ser Leu Ala Ser Leu Leu Gln Pro
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                    455
Ile Pro Phe Pro Lys Glu
465
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<213> Mouse
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Phe Phe Cys Glu Gly Val Lys Ile Ile Phe Arg Val Ala Leu Val Leu
                            25
          20
Leu Arg His Thr Leu Gly Ser Val Glu Lys Leu Arg Ser Cys Gln Gly
      35
                      40
                                          45
Met Tyr Glu Thr Met Glu Gln Leu Arg Asn Leu Pro Gln Gln Cys Met
   50
                    55
                                60
Gln Glu Asp Phe Leu Val His Glu Val Thr Asn Leu Pro Val Thr Glu
                                  75 · 80
             70
Ala Trp Ile Glu Arg Glu Asn Ala Ala Gln Leu Lys Lys Trp Arg Glu
            85
                             90
Thr Arg Gly Glu Leu Gln Tyr Arg Pro Ser Arg Arg Leu His Gly Ser
           100
                             105
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Arg Ala Ile His Glu Glu Arg Arg Arg Gln Gln Pro Pro Leu Gly Pro
  · 115
                       120
                                · 125
Ser Ser Ser Leu Leu Ser Leu Pro Ser Leu Lys Ser Arg Gly Ser Arg
 130
                   135
                                     140
Ala Val Gly Gly Ala Pro Ser Pro Pro Pro Pro Val Arg Arg Ala Ser
               150
                                 155
                                                   160
Ala Gly Pro Val Pro Gly Ala Val Val Ile Ala Glu Gly Leu His Pro
165 170 175
                                                175
Ser Leu Pro Ser Pro Thr Gly Asn Ser Thr Pro Leu Gly Thr Ser Lys
       180 185
Glu Ile Arg Arg Gln Glu Lys Glu Arg Gln Lys Gln Glu Lys Asp Arg
 195 200
                                 205
Glu Lys Glu Arg Gln Arg Gln Glu Lys Glu Arg Glu Arg Gln Glu Arg
210 215 220
Ser Gly Arg Ser Gly Lys Arg Ser Lys Arg Arg Asn Ser Arg Ser Arg 225 230 235 240
Arg Arg Ser Gly Arg Ser Trp Arg Arg Lys Ala Lys Ala Gly Asn Cys
                            250
             245
                                       255
Pro Cys Val Glu Gly Gln Met Gly Pro Arg His Pro Met Met Val Gly
        260
                  265 270
Thr Gly Gln Gln Leu Arg Pro Gly Arg Met Leu Thr Phe Asp Leu Trp
275 280 285
                                285
      275
                      280
Leu Asp Leu Asp Gly Met Ala Leu Leu Leu Pro Leu Ile Glu Ser Ser
                 295 300
Pro Gly Arg Leu Ser Gln Leu Pro Leu Ala Gly Ser Ser Phe Phe
305
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                                   315
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Met Phe Ser Glu Lys Lys His Phe Leu His Thr Ile Gln Asn Pro Glu
Ser Glu Lys Glu Arg Arg Arg Arg Arg Arg Arg Arg Ser Arg Arg
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                                          30
Arg Glu Arg Lys Lys Glu Arg Lys Lys Glu Arg Lys Glu Arg Lys
     35
                                         45
                        40
Gln Ala Ser Leu Pro Ser Val Lys Arg Glu Arg Ala Trp His Gly Glu
            55
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Gln Thr Gln Gly Ser Leu Ser Thr Val Arg Gln Glu Ser Ser Pro.Gly
65
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His Arg Ala Lys Val Ile Ala Asp Leu Gly Lys Asn Asp Gln
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Val Arg Trp Lys Met Arg Arg Ser Leu Arg Ala Gly Arg Arg Arg Gln
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Thr Ala Gly Arg Lys Ser Lys Ser Pro Pro Lys Val Pro Ile Val Ile
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                           25 ·
Gln Asp Asp Ser Leu Pro Thr Gly Pro Pro Pro Gln Ile Arg Ile Leu
```

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40
                                              45
Lys Arg Pro Thr Ser Asn Gly Val Val Ser Ser Pro Asn Ser Thr Ser
  50
                    55
                                        60
Arg Pro Ala Leu Pro Val. Lys Ser Leu Ala Gln Arg Glu Ala Glu Tyr
                  70
                                   75
Ala Glu Ala Arg Arg Ile Leu Gly Ser Ala Ser Pro Glu Glu Glu 85 90 95
Gln Glu Lys Pro Ile Leu Asp'Arg Pro Thr Arg Ile Ser Gln Pro Glu
         100 105 110
Asp Ser Arg Gln Pro Ser Asn Val Ile Arg Gln Pro Leu Gly Pro Asp
                        120
      115
Gly Ser Gln Gly Phe Lys Gln Arg Arg
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Glu Thr Thr Ile Thr Thr Asp Ser Arg Asp Tyr Gln Met Ala Lys Gly
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Lys Arg Lys Asn Leu Thr Asn Arg Asn Gln Asp His Ser Leu Ser Ser
  20
                             25
Glu Pro Ser Thr Pro Thr Ser Ala Ser Pro Gly Tyr Pro Asp Thr Pro
  35
                       40
                                            45
Glu Lys Gln Asp Ser Asn Leu Lys Ser Tyr Leu Met Met Leu Val Glu
50 55 60
Asp Ile Lys Lys Gly Phe Asn Asn Ser Leu Lys Glu Val Lys Glu Asn 65 70 75 80
Thr Ala Lys Glu Val Glu Val Leu Lys Glu Ile Gln Glu Asn Thr Thr
              85
                                90
Lys Gln Val Met Glu Leu Asn Lys Ile Ile Gln Asp Leu Lys Arg Glu
          100
                    105
                                              110
Val Glu Thr Lys Lys Thr Gln Asn Glu Thr Thr Leu Glu Ile Glu Thr
115 120 125
                         120
Leu Val Lys Lys Ser Gly Thr Ile Asp Val Ser Ile Ser Asn Arg Ile
  130
                   135
                                       140
Gln Glu Met Glu Glu Arg Ile Ser Gly Ala Glu Asp Ser Ile Glu Asn
                 150
                                    155
Ile Gly Thr Thr Thr Lys Glu Asn Ala Lys Arg Lys Lys Ile Leu Thr
             165
                         170
Gln Asn Ile Gln Lys Ile Gln Asp Lys Met Arg Arg Pro Asn Leu Trp
180 185 190
Ile Ile Gly Val Asp Glu Asn Glu Asp Ser Gln Leu Lys Gly Pro Ala
      195
                         200
                                      205<sup>.</sup>
Asn Ile Phe Asn Lys Phe Ile Glu Glu Asn Phe Pro Asn Leu Lys Lys
            215
                                  220
Glu Met Ser Met Asn Arg Gln Glu Ala Tyr Arg Thr Pro Asn Arg Leu
225 230 235 240
Asp Gln Lys Arg Asn Ser Ser Leu His Ile Ile Ile Arg Thr Thr Asn
             245
                       250
Ala Leu Asn Lys Asp Arg Ile Leu Lys Ala Val Arg Glu Lys Ser Gln
        260
                            265
Val Thr Tyr Lys Gly Arg Pro Ile Arg Ile Thr Pro Asp Phe Ser Pro
       275
                         280
                                            285
Glu Thr Met Lys Ala Arg Arg Ser Trp Thr Asp Val Met Gln Thr Leu
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300
   290
                   295
Arg Glu His Lys Cys Gln Pro Arg Leu Leu Tyr Pro Ala Lys Leu Ser 305 310 315 320
                             315
Ile Thr Ile Asp Gly Glu Thr Lys Val Phe His Asp Lys Thr Lys Phe
          325 330
                                     335
Thr Gln Tyr Leu Ser Met Asn Pro Gly Leu Gln Arg Ile Ile Lys Gly
340 350
Lys His Gln His Lys Asp Gly Asn Tyr Thr Leu Glu Lys Ala Arg Lys
 355 360 365
Arg Ser Phe Asn Lys Pro Lys Arg Arg Gln Pro Lys
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Tyr Gly Thr His Asn His Cys Trp Leu Ser Leu His Arg Gly Phe Ile
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Trp Ser Phe Leu Gly Pro Ala Ala Ile Ile Leu Ile Asn Leu Val
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                         25
Phe Tyr Phe Leu Ile Ile Trp Ile Leu Arg Ser Lys Leu Ser Ser Leu
                     40
    35
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Asn Lys Glu Val Ser Thr Leu Gln Asp Thr Lys Val Met Thr Phe Lys
          55
                              60
Ala Ile Val Gln Leu Phe Val Leu Gly Cys Ser Trp Gly Ile Gly Leu 65 70 75 80
Phe Ile Phe Ile Glu Val Gly Lys Thr Val Arg Leu Ile Val Ala Tyr
           85
                           90
Leu Phe Thr Ile Ile Asn Val Leu Gln Gly Val Leu Ile Phe Met Val
                         105
      100
                                   110
His Cys Leu Leu Asn Arg Gln Val Arg Met Glu Tyr Lys Lys Trp Phe
  115 120
                               125
His Arg Leu Arg Lys Glu Val Glu Ser Glu Ser Thr Glu Val Ser His
. 130 135 140
Ser Thr Thr His Thr Lys Met Gly Leu Ser Leu Asn Leu Glu Asn Phe
145 150 155
Cys Pro Thr Gly Asn Leu His Asp Pro Ser Asp Ser Ile Leu Pro Ser
         165 170
                                    175
Thr Glu Val Ala Gly Val Tyr Leu Ser Thr Pro Arg Ser His Met Gly
                185
       180
                                 190
Ala Glu Asp Val Asn Ser Gly Thr His Ala Tyr Trp Ser Arg Thr Ile
                      200
                                       205
Ser Asp
 210
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Met Lys Glu Tyr Val Met Leu Leu Leu Leu Ala Val Cys Ser Ala Lys
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                           10 15
Pro Phe Phe Ser Pro Ser His Thr Ala Leu Lys Asn Met Met Leu Lys
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35
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Leu Phe Pro Thr Lys Glu Pro Val Asn Pro Phe Phe Pro Phe Asp Leu
  50
                 55
                                 60
Phe Pro Thr Cys Pro Phe Gly Cys Gln Cys Tyr Ser Arg Val Val His
65
              70
                              75
Cys Ser Asp Leu Gly Leu Thr Ser Val Pro Asn Asn Ile Pro Phe Asp
          85
                          90
Thr Arg Met Val Asp Leu Gln Asn Asn Lys Ile Lys Glu Ile Lys Glu
                 105
       100
                                · 110
Asn Asp Phe Lys Gly Leu Thr Ser Leu Tyr Ala Leu Ile Leu Asn Asn
115 120 125
                              125
Asn Lys Leu Thr Lys Ile His Pro Lys Thr Phe Leu Thr Thr Lys Lys
  130 135
                                  140
Leu Arg Arg Leu Tyr Leu Ser His Asn Gln Leu Ser Glu Ile Pro Leu
145 150
                              155
Asn Leu Pro Lys Ser Leu Ala Glu Leu Arg Ile His Asp Asn Lys Val
        165
                          170
                                           175
Lys Lys Ile Gln Lys Asp Thr Phe Lys Gly Met Asn Ala Leu His Val
     . 180
                      185
                                 190
Leu Glu Met Ser Ala Asn Pro Leu Glu Asn Asn Gly Ile Glu Pro Gly
    195 200 205
Ala Phe Glu Gly Val Thr Val Phe His Ile Arg Ile Ala Glu Ala Lys
  210
                 215
                                220
Leu Thr Ser Ile Pro Lys Gly Leu Pro Pro Thr Leu Leu Glu Leu His
        230
                       235
Leu Asp Phe Asn Lys Ile Ser Thr Val Glu Leu Glu Asp Leu Lys Arg
           245
                    250
                                255
Tyr Arg Glu Leu Gln Arg Leu Gly Leu Gly Asn Asn Arg Ile Thr Asp
        260
                        265
Ile Glu Asn Gly Thr Phe Ala Asn Ile Pro Arg Val Arg Glu Ile His
             280
     275
                              285
290 295
Lys Tyr Leu Gln Ile Ile Phe Leu His Tyr Asn Ser Ile Ala Lys Val
305 310 315
Gly Val Asn Asp Phe Cys Pro Thr Val Pro Lys Met Lys Lys Ser Leu
           325
                   330 . 335
Tyr Ser Ala Ile Ser Leu Phe Asn Asn Pro Met Lys Tyr Trp Glu Ile
                345 350
Gln Pro Ala Thr Phe Arg Cys Val Leu Gly Arg Met Ser Val Gln Leu
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Gly Asn Val Gly Lys
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Met Trp Gly Cys Trp Leu Gly Leu Leu Leu Leu Leu Leu Ala Gly Gln
                            10
Ala Ala Leu Glu Ala Arg Arg Ser Arg Trp Arg Arg Glu Leu Ala Pro
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                       25
                                       30
Gly Leu His Leu Arg Gly Ile Arg Asp Ala Gly Gly Arg Tyr Cys Gln
                     40
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Glu Gln Asp Met Cys Cys Arg Gly Arg Ala Asp Glu Cys Ala Leu Pro
                     55
Tyr Leu Gly Ala Thr Cys Tyr Cys Asp Leu Phe Cys Asn Arg Thr Val
                 70
                                  75
Ser Asp Cys Cys Pro Asp Phe Trp Asp Phe Cys Leu Gly Ile Pro Pro
             85
                               90
Pro Phe Pro Pro Val Gln Gly Cys Met His Gly Gly Arg Ile Tyr Pro 100 105 110
Val Phe Gly Thr Tyr Trp Asp Asn Cys Asn Arg Cys Thr Cys His Glu
    115
                     120
                                         125
Gly Gly His Trp Glu Cys Asp Gln Glu Pro Cys Leu Val Asp Pro Asp
                  135
                                     140
Met Ile Lys Ala Ile Asn Arg Gly Asn Tyr Gly Trp Gln Ala Gly Asn 145 150 150 155
        150
                                  155
His Ser Ala Phe Trp Gly Met Thr Leu Asp Glu Gly Ile Arg Tyr Arg
             165
                             170
                                                175
Leu Gly Thr Ile Arg Pro Ser Ser Thr Val Met Asn Met Asn Glu Ile
          180
                          185
                                             190
Tyr Thr Val Leu Gly Gln Gly Glu Val Leu Pro Thr Ala Phe Glu Ala
      195
               200
                                  205
Ser Glu Lys Trp Pro Asn Leu Ile His Glu Pro Leu Asp Gln Gly Asn 210 215 220
Cys Ala Gly Ser Trp Ala Phe Ser Thr Ala Ala Val Ala Ser Asp Arg
225
        230
                                 235
Val Ser Ile His Ser Leu Gly His Met Thr Pro Ile Leu Ser Pro Gln
       245
                      250
                                         255
Asn Leu Leu Ser Cys Asp Thr His His Gln Gln Gly Cys Arg Gly Gly 260 265 270
Arg Leu Asp Gly Ala Trp Trp Phe Leu Arg Arg Arg Gly Val Val Ser
     275
                       280
Asp Asn Cys Tyr Pro Phe Ser Gly Arg Glu Gln Asn Glu Ala Ser Pro
  290
                  295
                                      300
Thr Pro Arg Cys Met Met His Ser Arg Ala Met Gly Arg Gly Lys Arg
             310
                                315
Gln Ala Thr Ser Arg Cys Pro Asn Gly Gln Val Asp Ser Asn Asp Ile
 . 325 330
                                        335
Tyr Gln Val Thr Pro Ala Tyr Arg Leu Gly Ser Asp Glu Lys Glu Ile
 . 340
                          345
                                             350
Met Lys Glu Leu Met Glu Asn Gly Pro Val Gln Ala Leu Met Glu Val
 355 360
                                 365
His Glu Asp Phe Phe Leu Tyr Gln Arg Gly Ile Tyr Ser His Thr Pro 370 375 380 ...
Val Ser Gln Gly Arg Pro Glu Gln Tyr Arg Arg His Gly Thr His Ser
               390
                                  395
Val Lys Ile Thr Gly Trp Gly Glu Glu Thr Leu Pro Asp Gly Arg Thr
             405
                               410
Ile Lys Tyr Trp Thr Ala Ala Asn Ser Trp Gly Pro Trp Trp Gly Glu
          420
                         425
                                     430
Arg Gly His Phe Arg Ile Val Arg Gly Thr Asn Glu Cys Asp Ile Glu
     435
                    440
                                445
Thr Phe Val Leu Gly Val Trp Gly Arg Val Gly Met Glu Asp Met Gly
                     455
 450
                                       460
His His
465
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Ala Pro Glu Val Cys Gly Ala Leu Asn Val Thr Val Ser Pro Gly Pro
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                              25
Val Val Asp Tyr Leu Glu Gly Glu Asn Ala Thr Leu Leu Cys His Val
      35
                          40
                                             45
Ser Gln Lys Arg Arg Lys Asp Ser Leu Leu Ala Val Arg Trp Phe Phe
                      55
                                         60
Ala Pro Asp Gly Ser Gln Glu Ala Leu Met Val Lys Met Thr Lys Leu
                70
                                   75
Arg Ile Ile Gln Tyr Tyr Gly Asn Phe Ser Arg Thr Ala Asn Gln Gln
             85
                            90
Arg Leu Arg Leu Leu Glu Glu Arg Arg Gly Val Leu Tyr Arg Leu Ser
           100
                             105
                                                 110
Val Leu Thr Leu Arg Pro Thr Asp Gln Gly Gln Tyr Val Cys Lys Val
                         120
                                            125
Gln Glu Ile Ser Lys His Arg Asn Lys Trp Thr Ala Trp Ser Asn Gly
  130
                      135
                                         140
Ser Ser Ala Thr Glu Met Arg Val Ile Ser Leu Lys Ala Gly Glu Asp
                  150
                                 155
Ser Ser Phe Glu Lys Lys Lys Val Thr Trp Ala Phe Phe Glu Asp Leu
165 170 175
Tyr Val Tyr Ala Val Leu Val Cys Cys Val Gly Ile Leu Ser Val Leu
         180
                             1.85
                                                 190
Leu Phe Thr Leu Val Ile Ala Cys Ser Leu Cys Phe Thr Arg Gly Asn
                          200
                                             205
Gln Glu
  210
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<213> Mouse
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Met Asp Phe Trp Leu Trp Leu Leu Tyr Phe Leu Pro Val Ser Gly Ala
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Leu Arg Val Leu Pro Glu Val Gln Leu Asn Val Glu Trp Gly Gly Ser
                             25
                                                 30
Ile Ile Ile Glu Cys Pro Leu Pro Gln Leu His Val Arg Met Tyr Leu
      35
                         40
                                            45
Cys Arg Gln Met Ala Lys Pro Gly Ile Cys Ser Thr Val Val Ser Asn.
  50
                      55 -
Thr Phe Val Lys Lys Glu Tyr Glu Arg Arg Val Thr Leu Thr Pro Cys
70 75 80
                                  75
Leu Asp Lys Lys Leu Phe Leu Val Glu Met Thr Gln Leu Thr Glu Asn
              85
                               90
                                                    95
Asp Asp Gly Ile Tyr Ala Cys Gly Val Gly Met Lys Thr Asp Lys Gly
                                         . 110
           100
                             105
Lys Thr Gln Lys Ile Thr Leu Asn Val His Asn Glu Tyr Pro Glu Pro
                        120 125
Phe Trp Glu Asp Glu Trp Thr Ser Glu Arg Pro Arg Trp Leu His Arg
   130
                      135
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Phe Leu Gln His Gln Met Pro Trp Leu His Gly Ser Glu His Pro Ser
                  150
                                   155
Ser Ser Gly Val Ile Ala Lys Val Thr Thr Pro Ala Ser Lys Thr Glu
              165
                              170
                                                175
Ala Pro Pro Val His Gln Pro Ser Ser Ile Thr Ser Val Thr Gln His
          180
                            185
                                      . 190
Pro Arg Val Tyr Arg Ala Phe Ser Val Ser Ala Thr Lys Ser Pro Ala
  195
               `200 205
Leu Leu Pro Ala Thr Thr Ala Ser Lys Thr Ser Thr Gln Gln Ala Ile
                   215
                                   220
Arg Pro Leu Glu Ala Ser Tyr Ser His His Thr Arg Leu His Glu Gln 225 230 230 240
Arg Thr Arg His His Gly Pro His Tyr Gly Arg Glu Asp Arg Gly
              245
                                250
                                                  255
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Met Lys Ala Leu Arg Ala Val Leu Leu Ile Leu Leu Leu Ser Gly Gln
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Pro Gly Ser Gly Trp Ala Gln Glu Asp Gly Asp Ala Asp Pro Glu Pro
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                          25`
                                              30
Glu Asn Tyr Asn Tyr Asp Asp Asp Asp Glu Glu Glu Glu Glu Glu
      35
                        40
                                         45
Thr Asn Met Ile Pro Gly Ser Arg Asp Arg Ala Pro Leu Gln Cys Tyr
                    55
                                     60
Phe Cys Gln Val Leu His Ser Gly Glu Ser Cys Asn Gln Thr Gln Ser
                 70
Cys Ser Ser Ser Lys Pro Phe Cys Ile Thr Leu Val Ser His Ser Gly
              85
                              90
Thr Asp Lys Gly Tyr Leu Thr Thr Tyr Ser Met Trp Cys Thr Asp Thr 100 105 110
Cys Gln Pro Ile Ile Lys Thr Val Gly Gly Thr Gln Met Thr Gln Thr
   115
                     120
                                         125
Cys Cys Gln Ser Thr Leu Cys Asn Ile Pro Pro Trp Gln Asn Pro Gln
 130
                  135
                              140
Thr Arg His Pro Gln Gly Gly Lys Phe Ser His Pro Gln Val Val Lys
            165
                              170
Ala Ala His Pro Gln Ser Asp Gly Ala Asn Leu Pro Lys Ser Gly Lys
          180
                            185
                                              190
Ala Asn Gln Pro Gln Gly Ser Gly Ala Gly Tyr Pro Ser Gly Trp Thr,
                                         205_-
   195
                        200
Lys Phe Gly Asn Ile Ala Leu Leu Leu Ser Phe Phe Thr Cys Leu Trp
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                     215
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Ala Ser Gly Ala
225
<210> 685
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<213> Mouse

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Met Ala Ser Gly Trp Phe Tyr Leu Ser Cys Met Val Leu Gly Ser Leu
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Gly Ser Met Cys Ile Leu Phe Thr Ala Tyr Trp Met Gln Tyr Trp Arg
          20
                            25
                                             30
Gly Gly Phe Ala Trp Asp Gly Thr Val Leu Met Phe Asn Trp His Pro
     35
                        40
Val Leu Met Val Ala Gly Met`Val Val Leu Tyr Gly Ala Ala Ser Leu
  50 55
                               60
Val Tyr Arg Leu Pro Ser Ser Trp Val Gly Pro Arg Leu Pro Trp Lys
65
               70
                                  75
Val Leu His Ala Ala Leu His Leu Leu Ala Phe Thr Cys Thr Val Val
            85 .
                              90 -
Gly Leu Ile Ala Val Phe Arg Phe His Asn His Ser Arg Ile Ala His
          100
                         105
                                            110
Leu Tyr Ser Leu His Ser Trp Leu Gly Ile Thr Thr Val Val Leu Phe
                      120
                                125
Ala Cys Gln Trp Phe Leu Gly Phe Ala Val Phe Leu Leu Pro Trp Ala
  130
                  135 ·
                                   140
Ser Gln Trp Leu Arg Ser Leu Leu Lys Pro Leu His Val Phe Phe Gly
145
        150
                         1.55
Ala Cys Ile Leu Ser Leu Ser Ile Thr Ser Val Ile Ser Gly Ile Asn
           165 170
Glu Lys Leu Phe Phe Val Leu Lys Asn Ala Thr Lys Pro Tyr Ser Ser
                           185
         180
                                         190
Leu Pro Gly Glu Ala Val Phe Ala Asn Ser Thr Gly Leu Leu Val Val
  195
                     200
                                         205
Ala Phe Gly Leu Leu Val Leu Tyr Val Leu Leu Ala Ser Ser Trp Lys
 210
                   215
                                     220
Arg Pro Asp Pro Gly Ala Leu Thr Asp Arg Gln Pro Leu Leu His Asp
                                  235
Arg Glu
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<213> Mouse
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Met Arg Leu Pro Leu Pro Leu Leu Leu Phe Gly Cys Arg Ala Ile
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Leu Gly Ser Ala Gly Asp Arg Val Ser Leu Ser Ala Ser Ala Pro Thr
        20
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Leu Asp Asp Glu Glu Lys Tyr Ser Ala His Met Pro Ala His Leu Arg
      35
                        40
                                        ·45
Cys Asp Ala Cys Arg Ala Val Ala Phe Gln Met Gly Gln Arg Leu Ala
  50
                  55
                                     60
Lys Ala Glu Ala Lys Ser His Thr Pro Asp Ala Ser Gly Leu Gln Glu
                 70
                                  75
Leu Ser Glu Ser Thr Tyr Thr Asp Val Leu Asp Gln Thr Cys Ser Gln
                             90
Asn Trp Gln Ser Tyr Gly Val His Glu Val Asn Gln Met Lys Arg Leu
         100
                          105
                                            110
Thr Gly Pro Gly Leu Ser Lys Gly Pro Glu Pro Arg Ile Ser Val Met
      115
                      120
                                        125
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Ile Ser Gly Gly Pro Trp Pro Asn Arg Leu Ser Lys Thr Cys Phe His

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130
                     135
                                       140
Tyr Leu Gly Glu Phe Gly Glu Asp Gln Ile Tyr Glu Ala Tyr Arg Gln
               150 . 155
Gly Gln Ala Asn Leu Glu Ala Leu Leu Cys Gly Gly Thr His Gly Pro
                          170
              165
Cys Ser Gln Glu Ile Leu Ala Gln Arg Glu Glu Leu
          180
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<210> 687
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<212> PRT
<213> Mouse
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Met Ile Pro Gln Val Val Thr Ser Glu Thr Val Thr Val Ile Ser Pro
1
              5
                               10
Asn Gly Ile Ser Phe Pro Gln Thr Asp Lys Pro Gln Pro Ser His Gln
         20
                            25
                                              30
Ser Gln Asp Arg Leu Lys Lys His Leu Lys Ala Glu Ile Lys Val Met
     35
                     40
                                          45
Ala Ala Ile Gln Ile Met Cys Ala Val Met Val Leu Ser Leu Gly Ile
                   55
                                      60 .
Ile Leu Ala Ser Val Pro Ser Asn Leu His Phe Thr Ser Val Phe Ser
               70
                                75
Ile Leu Leu Glu Ser Gly Tyr Pro Phe Val Gly Ala Leu Phe Phe Ala
             85
                              . 90
Ile Ser Gly Ile Leu Ser Ile Val Thr Glu Lys Lys Met Thr Lys Pro
                           105
                                             110
Leu Val His Ser Ser Leu Ala Leu Ser Ile Leu Ser Val Leu Ser Ala
      115
                        120
Leu Thr Gly Ile Ala Ile Leu Ser Val Ser Leu Ala Ala Leu Glu Pro
                    135
  130
                                      140
Ala Leu Gln Gln Cys Lys Leu Ala Phe Thr Gln Leu Asp Thr Thr Gln
                150
                                 155
                                                     160
Asp Ala Tyr His Phe Phe Ser Pro Glu Pro Leu Asn Ser Cys Phe Val
             165
                              170
                                                 175
Ala Lys Ala Ala Leu Thr Gly Val Phe Ser Leu Met Leu Ile Ser Ser
. 180
                          185
                                     190
Val Leu Glu Leu Gly Leu Ala Val Leu Thr Ala Thr Leu Trp Trp Lys
                        200
  195
                                          205
Gln Ser Ser Ser Ala Phe Ser Gly Asn Val Ile Phe Leu Ser Gln Asn
            215
                                      220
Ser Lys Asn Lys Ser Ser Val Ser Ser Glu Ser Leu Cys Asn Pro Thr
225 230
                                   235
Tyr Glu Asn Ile Leu Thr Ser
              245
<210> 688
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<213> Mouse
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Tyr Gln Arg Arg Ser Lys Thr Leu Glu Glu Leu Ala Asn Asp Ile Lys
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Glu Asp Ala Ile Ala Pro Arg Thr Leu Pro Trp Thr Lys Gly Ser Asp
       . 20
                            25.
                                              30
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Thr Ile Ser Lys Asn Gly Thr Leu Ser Ser Val Thr Ser Ala Arg Ala
                        40
                                       45
Leu Arg Pro Pro Lys Ala Ala Pro Pro Arg Pro Gly Thr Phe Thr Pro
  50
                   55
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Thr Pro Ser Val Ser Ser Gln Ala Leu Ser Ser Pro Arg Leu Pro Arg
               70
                                 75
Val Asp Glu Pro Pro Pro Gln Ala Val Ser Leu Thr Pro Gly Gly Val
85 90 95
Ser Ser Ser Ala Leu Ser Arg Met Gly Ala Val Pro Val Met Val Pro
      100
                105
Ala Gin Ser Gin Ala Gly Ser Leu Val
     115
                      120
<210> 689
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<213> Mouse
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Pro Ala Phe Ser Ser Ala Ala Met Ser Trp Ser Pro Ile Leu Pro Phe 1 5 10 . 15
Leu Ser Leu Leu Leu Leu Phe Pro Leu Glu Val Pro Arg Ala Ala
 20
                         25
                                           30
Thr Ala Ser Leu Ser Gln Ala Ser Ser Glu Gly Thr Thr Thr Cys Lys
  35
                      40
                                        45
Val His Asp Val Cys Leu Leu Gly Pro Arg Pro Leu Pro Pro Ser Pro
 50 55
                                  60
Pro Val Arg Val Ser Leu Tyr Tyr Glu Ser Leu Cys Gly Ala Cys Arg
       70
                          75
Tyr Phe Leu Val Arg Asp Leu Phe Pro Thr Trp Leu Met Val Met Glu
           85
                     90
Ile Met Asn Ile Thr Leu Val Pro Tyr Gly Asn Ala Gln Glu Arg Asn
         100
                         105
Val Ser Gly Thr Trp Glu Phe Thr Cys Gln His Gly Glu Leu Glu Cys
115 120 125
Arg Leu Asn Met Val Glu Ala Cys Leu Leu Asp Lys Leu Glu Lys Glu
  130 135 140
Ala Ala Phe Leu Thr Ile Val Cys Met Glu Glu Met Asp Asp Met Glu
                               155
145 150
Lys Lys Leu Gly Pro Cys Leu Gln Val Tyr Ala Pro Glu Val Ser Pro
                      170
        165
                                              175
Glu Ser Ile Met Glu Cys Ala Thr Gly Lys Arg Gly Thr Gln Leu Met
180 185 190
His Glu Asn Ala Gln Leu Thr Asp Ala Leu His Pro Pro His Glu Tyr
    195 200 205
Val Pro Trp Val Leu Val Asn Glu Lys Pro Leu Lys Asp Pro Ser Glu
  210 .
                 215
                                   220
Leu Leu Ser Ile Val Cys Gln Leu Asp Gln Gly Thr Glu Lys Pro Asp
225 230
                                235 240
Ile Cys Ser Ser Ile Ala Asp Ser Pro Arg Lys Val Cys Tyr Lys
             245
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<210> 690
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Met Val Trp Thr Gln Asp Arg Leu His Asp Arg Gln Arg Val Val His
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Trp Asp Leu Ser Gly Asp Pro Gly Ser Gln Arg Arg Arg Leu Val Asp
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Met Tyr Ser Ala Gly Glu Gln Arg Val Tyr Glu Pro Arg Asp Arg Asp
     35
                                         45
Arg Leu Leu Ser Pro Ser Ala Phe His Asp Gly Asn Phe Ser Leu
  <sup>-</sup>50
                  55
                                     60
Leu Ile Arg Ala Val Glu Arg Gly Asp Glu Gly Val Tyr Thr Cys Asn
               70
                                   75
Leu His His His Tyr Cys His Leu Asp Glu Ser Leu Ala Val Arg Leu
            85
                               90
Glu Val Thr Asp Asp Pro Leu Leu Ser Arg Ala Tyr Trp Asp Gly Glu
100 105 110
Lys Glu Val Leu Val Val Ala His Gly Ala Pro Ala Leu Met Thr Cys
                        120
   115
                                         125
Ile Asn Arg Ala His Val Trp Thr Asp Arg His Leu Glu Glu Ala Gln
          . 135
  130
                              140
Gln Val Val His Trp Asp Arg Gln Leu Pro Gly Val Ser His Asp Arg 145 150 150 155 160
Ala Asp Arg Leu Leu Asp Leu Tyr Ala Ser Gly Glu Arg Arg Ala Tyr
            165 170
Gly Pro Pro Phe Leu Arg Asp Arg Val Ser Val Asn Thr Asn Ala Phe
          180
                          185
                                     190
Ala Arg Gly Asp Phe Ser Leu Arg Ile Asp Glu Leu Glu Arg Ala Asp
      195
                200
                                  205
Glu Gly Ile Tyr Ser Cys His Leu His His His Tyr Cys Gly Leu His
            215
  210
                                220
Glu Arg Arg Val Phe His Leu Gln Val Thr Glu Pro Ala Phe Glu Pro
225
       230
                                  235
Pro Ala Arg Ala Ser Pro Gly Asn Gly Ser Gly His Ser Ser Ala
           245
                                250
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Met Lys Leu Lys Gln Arg Val Val Leu Leu Ala Ile Leu Leu Val Ile 1 5 10 15
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Phe Ile Phe Thr Lys Val Phe Leu Ile Asp Asn Leu Asp Thr Ser Ala
        20
                           25
Ala Asn Arg Glu Asp Gln Arg Ala Phe His Arg Met Met Thr Gly Leu
      35
                        40
                                          45
Arg Val Glu Leu Val Pro Lys Leu Asp His Thr Leu Gln Ser Pro Trp
                   55
                                    60
Glu Ile Ala Ala Gln Trp Val Val Pro Arg Glu Val Tyr Pro Glu Glu 65 70 75 80
                                   75
Thr Pro Glu Leu Gly Ala Ile Met His Ala Met Ala Thr Lys Lys Ile
            85
                             90
Ile Lys Ala Asp Val Gly Tyr Lys Gly Thr Gln Leu Lys Ala Leu Leu
          100
                           105
                                             110
Ile Leu Glu Gly Gly Gln Lys Val Val Phe Lys Pro Lys Arg Tyr Ser
```

120 Arg Asp Tyr Val Val Glu Gly Glu Pro Tyr Ala Gly Tyr Asp Arg His

115

```
130
                       135
                                          140
Asn Ala Glu Val Ala Ala Phe His Leu Asp Arg Ile Leu Gly Phe Arg
145 . 150 155
Arg Ala Pro Leu Val Val Gly Arg Tyr Val Asn Leu Arg Thr Glu Val
     165
                          170
Lys Pro Val Ala Thr Glu Gln Leu Leu Ser Thr Phe Leu Thr Val Gly 180 185 190
Asn Asn Thr Cys Phe Tyr Gly Lys Cys Tyr Tyr Cys Arg Glu Thr Glu
195 200 205
Pro Ala Cys Ala Asp Gly Asp Met Met Glu Gly Ser Val Thr Leu Trp
  210
                      215
                                     220
Leu Pro Asp Val Trp Pro Leu Gln Lys His Arg His Pro Trp Gly Arg
                 230
                            235
Thr Tyr Arg Glu Gly Lys Leu Ala Arg Trp Glu Tyr Asp Glu Ser
               245
                                  250
<210> 692
<211> 255
<212> PRT
<213> Mouse
<400> 692
Met Gln Thr Met Trp Gly Ser Gly Glu Leu Leu Val Ala Trp Phe Leu
               5
Val Leu Ala Ala Asp Gly Thr Thr Glu His Val Tyr Arg Pro Ser Arg
       20
                              25
Arg Val Cys Thr Val Gly Ile Ser Gly Gly Ser Ile Ser Glu Thr Phe 35 40 45
Val Gln Arg Val Tyr Gln Pro Tyr Leu Thr Thr Cys Asp Gly His Arg 50 55 60
 50 55
Ala Cys Ser Thr Tyr Arg Thr Ile Tyr Arg Thr Ala Tyr Arg Arg Ser 65 70 75 80
Pro Gly Val Thr Pro Ala Arg Pro Arg Tyr Ala Cys Cys Pro Gly Trp
            85
                                90
                                                   95
Lys Arg Thr Ser Gly Leu Pro Gly Ala Cys Gly Ala Ala Ile Cys Gln 100 105 110
Pro Pro Cys Gly Asn Gly Gly Ser Cys Ile Arg Pro Gly His Cys Arg
Cys Pro Val Gly Trp Gln Gly Asp Thr Cys Gln Thr Asp Val Asp Glu
 130
                   135
                                     140
Cys Ser Thr Gly Glu Ala Ser Cys Pro Gln Arg Cys Val Asn Thr Val
145 150 155 __160
Gly Ser Tyr Trp Cys Gln Gly Trp Glu Gly Gln Ser Pro Ser Ala Asp
165 170 175
Gly Thr Arg Cys Leu Ser Lys Glu Gly Pro Ser Pro Val Ala Pro Asn
          180
                            185
                                     190
Pro Thr Ala Gly Val Asp Ser Met Ala Arg Glu Glu Val Tyr Arg Leu
     195 . 200
                                           205
Gln Ala Arg Val Asp Val Leu Glu Gln Lys Leu Gln Leu Val Leu Ala
210 215 220
Pro Leu His Ser Leu Ala Ser Arg Ser Thr Glu His Gly Leu Gln Asp
                230
                            235
Pro Gly Ser Leu Leu Ala His Ser Phe Gln Gln Leu Asp Arg Ile
              245
                                  250
<210> 693
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<211> 255

<212> PRT <213> Mouse <400> 693 Met Arg Leu Thr Val Gly Ala Leu Leu Ala Cys Ala Ala Leu Gly Leu 10 Cys Leu Ala Val Pro Asp Lys Thr Val Lys Trp Cys Ala Val Ser Glu 20 25 30 His Glu Asn Thr Lys Cys Ile Ser Phe Arg Asp His Met Lys Thr Val 45 35 40 Leu Pro Pro Asp Gly Pro Arg Leu Ala Cys Val Lys Lys Thr Ser Tyr 55 Pro Asp Cys Ile Lys Ala Ile Ser Ala Ser Glu Ala Asp Ala Met Thr 70 75 Leu Asp Gly Gly Trp Val Tyr Asp Ala Gly Leu Thr Pro Asn Asn Leu 85 90 Lys Pro Val Ala Ala Glu Phe Tyr Gly Ser Val Glu His Pro Gln Thr 100 105 110 Tyr Tyr Tyr Ala Val Ala Val Val Lys Lys Gly Thr Asp Phe Gln Leu 115 120 125 Asn Gln Leu Glu Gly Lys Lys Ser Cys His Thr Gly Leu Gly Arg Ser 130 135 140 Ala Gly Trp Val Ile Pro Ile Gly Leu Leu Phe Cys Lys Leu Ser Glu 150 155 Pro Arg Ser Pro Leu Glu Lys Ala Val Ser Ser Phe Phe Ser Gly Ser 170 175 165 Cys Val Pro Cys Ala Asp Pro Val Ala Phe Pro Lys Leu Cys Gln Leu 180 185 190 Cys Pro Gly Cys Gly Cys Ser Ser Thr Gln Pro Phe Phe Gly Tyr Val 200 205 195 Gly Ala Phe Lys Cys Leu Lys Asp Gly Gly Gly Asp Val Ala Phe Val 210 ' 215 220 Lys His Thr Thr Ile Phe Glu Val Leu Pro Glu Lys Ala Asp Arg Asp 235 230 Gln Tyr Glu Leu Leu Cys Leu Asp Asn Thr Arg Lys Pro Val Asp 250 255 <210> 694 <211> 255 <212> PRT <213> Mouse <400> 694 Gly Ala Pro Thr Pro Ala Tyr Val Arg Ser Ala Arg Arg Thr Glu Pro 10 · 15 Leu Ala Ser Gly Ala Arg Ser Arg Leu Cys Gln Cys Arg Arg Val Pro 20 25 - .30 Ala Arg Lys Gln Gly Pro Gln Glu Gln Gly Gly Ser Gly Glu Ser Thr 45 35 40 Thr Ser Ser Pro Gln Trp Trp Arg Arg Trp Arg Arg Leu Trp Ser Thr 55 50 60 Cys Ser Cys Ser Ala Asp Asp Arg His Thr Gly Ser His Thr Asp Leu 70 75 Lys Glu Glu Thr Pro Ser Trp Thr Gln Ile Ser Val Val Phe Arg Lys 85 90 95

110

Asp Gly Gln Asp Glu Leu Gln Ala Ala His Lys Ala His Gly Ser Gly 105

Ser Pro Leu Thr Asn Gln Glu Ile Pro Ser Ser Ser Gly Ser Gly Phe

125

120

115

```
Ile Val Ser Glu Asp Gly Leu Ile Val Thr Asn Ala His Val Leu Thr
  130
                     135
                                     140
Asn Gln Gln Lys Ile Gln Val Glu Leu Gln Ser Gly Ala Arg Tyr Glu
               150
                              155
Ala Thr Val Lys Asp Ile Asp His Lys Leu Asp Leu Ala Leu Ile Lys
165 170 175
              165
                               170
                                         175
Ile Glu Pro Asp Thr Glu Leu Pro Val Leu Leu Gly Arg Ser Ser
         180
                           185
                                     190
Asp Leu Arg Ala Gly Glu Phe Val Val Ala Leu Gly Ser Pro Phe Ser
  195
                      200
                                           205
Leu Gln Asn Thr Val Thr Ala Gly Ile Val Ser Thr Thr Gln Arg Gly 210 215 220
Gly Arg Glu Leu Gly Leu Lys Asn Ser Asp Ile Asp Tyr Ile Gln Thr
225 230
                          235
Asp Ala Ile Ile Asn His Gly Asn Ser Gly Gly Pro Leu Val Asn
              245
                                 250
<210> 695
<211> 174
<212> PRT
<213> Mouse
<400> 695
Met Pro Ala Cys Arg Leu Cys Leu Leu Ala Ala Gly Leu Leu Gly
              5
                                10
Leu Leu Leu Phe Thr Pro Ile Ser Ala Thr Gly Thr Asp Ala Glu Lys
       20
                             25
                                              30
Pro Gly Glu Cys Pro Gln Leu Glu Pro Ile Thr Asp Cys Val Leu Glu
                       40
                                          45
Cys Thr Leu Asp Lys Asp Cys Ala Asp Asn Arg Lys Cys Cys Gln Ala
  50
                     55
                                       60
Gly Cys Ser Ser Val Cys Ser Lys Pro Asn Gly Pro Ser Glu Gly Glu
65
                70
                                  75
Leu Ser Gly Thr Asp Thr Lys Leu Ser Glu Thr Gly Thr Thr Thr Gln
             85
                               90
Ser Ala Gly Leu Asp His Thr Thr Lys Pro Pro Gly Gly Gln Val Ser
          100
                           105
                                              110
Thr Lys Pro Pro Ala Val Thr Arg Glu Gly Leu Gly Val Arg Glu Lys
     115
                      120
                                           125
Gln Gly Thr Cys Pro Ser Val Asp Ile Pro Lys Leu Gly Leu Cys Glu
  130
                   135
                                      140
Asp Gln Cys Gln Val Asp Ser Gln Cys Ser Gly Asn Met Lys Cys Cys
         150
                           155
Arg Asn Gly Cys Gly Lys Met Ala Cys Thr Thr Pro Lys Phe
             165
                                170
<210> 696
<211> 193
<212> PRT
<213> Mouse
<400> 696
Leu Ala Thr Leu Val Gln Val Ser Arg Ile Arg Ala Tyr Ser Gln Gly
            5
                             10
Gln Thr Gln Asp Gln Gln Gly Ser Ser Ser Leu Asp Lys Val Ala Val
```

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20
Pro Arg Glu Gln Thr His Ser Gly Leu Glu Gln Ile Gln Gln Ile Gln
  35
                         40
Gln Gln Leu Thr Gln Phe Asn Ala Ser Leu Ala Gly Leu Cys Arg Pro
  50
                     55
Cys Pro Trp Asp Trp Glu Leu Phe Gln Gly Ser Cys Tyr Leu Phe Ser 65 75 80
Arg Thr Leu Gly Ser Trp Glu Thr Ser Ala Ser Ser Cys Glu Asp Leu
             85
                             90
Gly Ala His Leu Val Ile Val Asn Ser Val Ser Glu Gln Arg Phe Met
        100
                   105
                                               110
Lys Tyr Trp Asn Val Arg Lys Asn Gln Arg Ser Trp Ile Gly Leu Ser
115 120 125
Asp His Ile His Glu Gly Ser Trp Gln Trp Val Asp Gly Ser Ala Leu
  130 · 135
                                     140
Lys Phe Ser Phe Trp Lys Glu Gly Glu Pro Asn Asn Asp Gly Asp Glu
                150
                              155
Asp Cys Val Glu Leu Phe Met Asp Asp Trp Asn Asp Asn Lys Cys Thr
             165
                               170
                                                  175
Glu Gln Asn Phe Trp Val Cys Glu Gln Pro Ser Ala Pro Cys Pro His
           180
                              185
<210> 697
<211> 173
<212> PRT
<213> Mouse
<400> 697
Val Arg Asn Gly Asp Leu Phe Phe Lys Lys Val Gln Val Glu Asp Gly
                                10
Gly Val Tyr Thr Cys Tyr Ala Met Gly Glu Thr Phe Asn Glu Thr Leu
        20
                            25
Ser Val Glu Leu Lys Val Tyr Asn Phe Thr Leu His Gly His His Asp
    35
                        40
                                           45
Thr Leu Asn Thr Ala Tyr Thr Thr Leu Val Gly Cys Ile Leu Ser Val
. 50
                    55
                                       60
Val Leu Val Leu Ile Tyr Leu Tyr Leu Thr Pro Cys Arg Cys Trp Cys 65 70 75 80
Arg Gly Val Glu Lys Pro Ser Ser His Gln Gly Asp Ser Leu Ser Ser 85 90 95
Ser Met Leu Ser Thr Thr Pro Asn His Asp Pro Met Ala Gly Gly Asp
                                     · 110
         100
                       105
Lys Asp Asp Gly Phe Asp Arg Arg Val Ala Phe Leu Glu Pro Ala Gly
     115
                        120
                                           125
Pro Gly Gln Gly Gln Asn Gly Lys Leu Lys Pro Gly Asn Thr Leu Pro
  130
                   135
                               140
Val Pro Glu Ala Thr Gly Lys Gly Gln Arg Arg Met Ser Asp Pro Glu
                 150
                                   155
Ser Val Ser Ser Val Phe Ser Asp Thr Pro Ile Val Val
              165
                                 170
<210> 698
<211> 88
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<212> PRT <213> Mouse

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<400> 698
Met Glu Glu Ile Thr Cys Ala Phe Leu Leu Leu Ala Gly Leu Pro
                                  10
Ala Leu Glu Ala Ser Asp Pro Val Asp Lys Asp Ser Pro Phe Tyr Tyr
           20
                             25
                                                 30
Asp Trp Glu Ser Leu Gln Leu Gly Gly Leu Ile Phe Gly Gly Leu Leu
                         `40
                                             45
Cys Ile Ala Gly Ile Ala Met Ala Leu Ser Gly Lys Cys Lys Cys Arg
                       55
                                         60
Arg Thr His Lys Pro Ser Ser Leu Pro Gly Lys Ala Thr Pro Leu Ile
                  70
Ile Pro Gly Ser Ala Asn Thr Cys
               85
<210> 699
<211> 155
<212> PRT
<213> Mouse
<400> 699
Met Tyr Ser Glu Gly Ala Pro Phe Trp Thr Gly Ile Val Ala Met Leu
1
                5
                                  1.0
Ala Gly Ala Val Ala Phe Leu His Lys Lys Arg Gly Gly Thr Cys Trp
          20
                              25
                                                  30
Ala Leu Met Arg Thr Leu Leu Val Leu Ala Ser Phe Cys Thr Ala Val
      35
                          40
Ala Ala Ile Val Ile Gly Ser Arg Glu Leu Asn Tyr Tyr Trp Tyr Phe
  50
                    · 55
                                         60
Leu Gly Asp Asp Val Cys Gln Arg Asp Ser Ser Tyr Gly Trp Ser Thr
                 .70
65 .
                                     75
Met Pro Arg Thr Thr Pro Val Pro Glu Glu Ala Asp Arg Ile Ala Leu
            85
                                 90
Cys Ile Tyr Tyr Thr Ser Met Leu Lys Thr Leu Leu Met Ser Leu Gln
           100
                             105
                                                110
Ala Met Leu Leu Gly Ile Trp Val Leu Leu Leu Leu Ala Ser Leu Thr
                        120
                                        125
Pro Val Cys Val Tyr Ile Trp Lys Arg Phe Phe Thr Lys Ala Glu Thr
  130
                      135
Glu Glu Lys Lys Leu Leu Gly Ala Ala Val Ile
                   150
145
<210> 700
<211> 255
<212> PRT
<213> Mouse
<400> 700
Met Leu Gln His Thr Ser Leu Val Leu Leu Leu Ala Ser Ile Trp Thr
               5 .
1
                                  10
Thr Arg His Pro Val Gln Gly Ala Asp Leu Val Gln Asp Leu Ser Ile
          20
                              25
Ser Thr Cys Arg Ile Met Gly Val Ala Leu Val Gly Arg Asn Lys Asn
                         40
Pro Gln Met Asn Phe Thr Glu Ala Asn Glu Ala Cys Lys Met Leu Gly
                       55
                                         60
Leu Thr Leu Ala Ser Arg Asp Gln Val Glu Ser Ala Gln Lys Ser Gly
```

65

```
70
                                                         80
Phe Glu Thr Cys Ser Tyr Gly Trp Val Gly Glu Gln Phe Ser Val Ile
               85
                                 90
Pro Arg Ile Phe Ser Asn Pro Arg Cys Gly Lys Asn Gly Lys Gly Val
         100
                    105
                                                 110
Leu Ile Trp Asn Ala Pro Ser Ser Gln Lys Phe Lys Ala Tyr Cys His
115 120 125

Asn Ser Ser Asp Thr Trp Val Asn Ser Cys Ile Pro Glu Ile Val Thr
  130 135
                                      140
Thr Phe Tyr Pro Val Leu Asp Thr Gln Thr Pro Ala Thr Glu Phe Ser
145
                 150
                                     155
Val Ser Ser Ser Ala Tyr Leu Ala Ser Ser Pro Asp Ser Thr Thr Pro
             165
                               170
                                                    175
Val Ser Ala Thr Thr Arg Ala Pro Pro Leu Thr Ser Met Ala Arg Lys
         180
                             185
                                        190
Thr Lys Lys Ile Cys Ile Thr Glu Val Tyr Thr Glu Pro Ile Thr Met
     195
                         200
                                            205
Ala Thr Glu Thr Glu Ala Phe Val Ala Ser Gly Ala Ala Phe Lys Asn
  210
                      215
                                         220
Glu Ala Ala Gly Phe Gly Gly Val Pro Thr Ala Leu Leu Val Leu Ala
225
                 230
                             235
Leu Leu Phe Phe Gly Ala Ala Ala Val Leu Ala Val Cys Tyr Val
               245
                                  250
<210> 701
<211> ·91
<212> PRT
<213> Mouse
<400> 701
Met Val Trp Ala Asn Leu Ala Val Phe Val Ile Cys Phe Leu Pro Leu
               5
                                 10
His Val Val Leu Thr Val Gln Val Ser Leu Asn Leu Asn Thr Cys Ala
        20
                             25
                                                 30
Ala Arg Asp Thr Phe Ser Arg Ala Leu Ser Ile Thr Gly Lys Leu Ser
      35
                         40
                                            45
Asp Thr Asn Cys Cys Leu Asp Ala Ile Cys Tyr Tyr Tyr Met Ala Arg
 · 50
                     55
                                        60
Glu Phe Gln Glu Ala Ser Lys Pro Ala Thr Ser Ser Asn Thr Pro His
                  70
Lys Ser Gln Asp Ser Gln Ile Leu Ser Leu Thr
               85
<210> 702
<211> 244
<212> PRT
<213> Mouse
<400> 702
Gly Trp Gln Gly Ala Pro Asp Pro Arg Gly Leu Gly Gln Leu Ser Gln
              5
                                 10
Pro Tyr Met Gly Gly Glu Met Pro Trp Thr Ile Leu Leu Phe Ala Ser
          20
                             25
                                         · 30
Gly Ser Leu Ala Ile Pro Ala Pro Ser Ile Ser Leu Val Pro Pro Tyr
     35
                       40 45
Pro Ser Ser His Glu Asp Pro Ile Tyr Ile Ser Cys Thr Ala Pro Gly
   50
```

```
Asp Ile Leu Gly Ala Asn Phe Thr Leu Phe Arg Gly Gly Glu Val Val
                 70 -
                                  75
Gln Leu Leu Gln Ala Pro Ser Asp Arg Pro Asp Val Thr Phe Asn Val
             85
                             90
Thr Gly Gly Gly Gly Gly Gly Glu Ala Ala Gly Gly Asn Phe
         100
                        105
Cys Cys Gln Tyr Gly Val Met Gly Glu His Ser Gln Pro Gln Leu Ser
115 120 125
Asp Phe Ser Gln Gln Val Gln Val Ser Phe Pro Val Pro Thr Trp Ile
 130 135
                              140
Leu Ala Leu Ser Leu Ser Leu Ala Gly Ala Val Leu Phe Ser Gly Leu
       150
                         155
Val Ala Ile Thr Val Leu Val Arg Lys Ala Lys Ala Lys Asn Leu Gln
165 170 175
Lys Gln Arg Glu Arg Glu Ser Cys Trp Ala Gln Ile Asn Phe Thr Asn
         180
                          185
Thr Asp Met Ser Phe Asp Asn Ser Leu Phe Ala Ile Ser Thr Lys Met
      195
                     200
                                        205
Thr Gln Glu Asp Ser Val Ala Thr Leu Asp Ser Gly Pro Arg Lys Arg
 210 215
                             220
Pro Thr Ser Ala Ser Ser Ser Pro Glu Pro Pro Glu Phe Ser Thr Phe
225 · 230
                                  235
Arg Ala Cys Gln
<210> 703
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<210> 703 <211> 255 <212> PRT <213> Mouse

50 55 60 60

Trp Met Lys Lys Asp Ser Gly Gly Ser His Ala Leu Val Ala Val Phe 65 70 70 75 80

His Pro Lys Lys Gly Pro Asn Ile Lys Glu Pro Glu Arg Val Lys Phe 85 90 95

Leu Ala Ala Gln Gln Asp Leu Arg Asn Ala Ser Leu Ala Ile Ser Asn 100 105 110 Leu Ser Val Glu Asp Glu Gly Ile Tyr Glu Cys Gln Ile Ala Thr Phe

Pro Arg Gly Ser Arg Ser Thr Asn Ala Trp Leu Lys Val Gln Ala Arg
130 135 140

Pro Lys Asn Thr Ala Glu Ala Leu Glu Pro Ser Pro Thr Leu Ile Leu 145 150 155 160

Gln Asp Val Ala Lys Cys Ile Ser Ala Asn Gly His Pro Pro Gly Arg 165 170 175 Ile Ser Trp Pro Ser Asn Val Asn Gly Ser His Arg Glu Met Lys Glu

180 185 190

Pro Gly Ser Gln Pro Gly Thr Thr Thr Val Thr Ser Tyr Leu Ser Met
195 200 205

```
Val Pro Ser Arg Gln Ala Asp Gly Lys Asn Ile Thr Cys Thr Val Glu
  210
                    215
                                      220
His Glu Ser Leu Gln Glu Leu Asp Gln Leu Leu Val Thr Leu Ser Gln
225
                 230
                                  235
Pro Tyr Pro Pro Glu Asn Val Ser Ile Ser Gly Tyr Asp Gly Asn
              245
                                250 .
                                                  255
<210> 704
<211> 255
<212> PRT
<213> Mouse
<400> 704
Met Phe Leu Val Gly Ser Leu Val Val Leu Cys Gly Leu Leu Ala His
 1
              5
                                10
                                           - 15
Ser Thr Ala Gln Leu Ala Gly Leu Pro Leu Pro Leu Gly Gln Gly Pro
  20
                           25
Pro Leu Pro Leu Asn Gln Gly Pro Pro Leu Pro Leu Asn Gln Gly Gln
 35
                        40
Leu Leu Pro Leu Ala Gln Gly Leu Pro Leu Ala Val Ser Pro Ala Leu
           55
 50
                                60
Pro Ser Asn Pro Thr Asp Leu Leu Ala Gly Lys Phe Thr Asp Ala Leu
65 70
                                   75
Ser Gly Gly Leu Leu Ser Gly Gly Leu Leu Gly Ile Leu Glu Asn Ile
             85
                               90
                                                 95
Pro Leu Leu Asp Val Ile Lys Ser Gly Gly Gly Asn Ser Asn Gly Leu
         100
                          105 . 110
Val Gly Gly Leu Leu Gly Lys Leu Thr Ser Ser Val Pro Leu Leu Asn
      115
                        120
                                  125
Asn Ile Leu Asp Ile Lys Ile Thr Asp Pro Gln Leu Leu Glu Leu Gly
  130
                    135
                                    140
Leu Val Gln Ser Pro Asp Gly His Arg Leu Tyr Val Thr Ile Pro Leu
145
               150
                                 155
                                                   160
Gly Leu Thr Leu Asn Val Asn Met Pro Val Val Gly Ser Leu Leu Gln 165 170 175
Leu Ala Val Lys Leu Asn Ile Thr Ala Glu Val Leu Ala Val Lys Asp
        180
                                   190
                            185
Asn Gln Gly Arg Ile His Leu Val Leu Gly Asp Cys Thr His Ser Pro
      195
                       200
                                          205
Gly Ser Leu Lys Ile Ser Leu Leu Asn Gly Val Thr Pro Val Gln Ser
  210
                    215 .220
Phe Leu Asp Asn Leu Thr Gly Ile Leu Thr Lys Val Leu Pro Glu Leu
225 230
                                 235
Ile Gln Gly Lys Val Cys Pro Leu Val Asn Gly Ile Leu Ser Gly
245 250 255
                              250
             245
                                                255
<210> 705
<211> 255
<212> PRT
<213> Mouse
<400> 705
Met Ala Thr Thr Thr Cys Gln Val Val Gly Leu Leu Leu Ser Leu Leu
              5
                               10
Gly Leu Ala Gly Cys Ile Ala Ala Thr Gly Met Asp Met Trp Ser Thr
                                           . 30
          20
                            25
Gln Asp Leu Tyr Asp Asn Pro Val Thr Ala Val Phe Gln His Glu Gly
```

40

```
Leu Trp Arg Ser Cys Val Gln Gln Ser Ser Gly Phe Thr Glu Cys Arg
  50
                    55
                                        60
Pro Tyr Phe Thr Ile Leu Gly Leu Pro Ala Met Leu Gln Ala Val Arg
                  70
                                     75
Ala Leu Met Ile Val Gly Ile Val Leu Gly Val Ile Gly Ile Leu Val
85 90 95
Ser Ile Phe Ala Leu Lys Cys'Ile Arg Ile Gly Ser Met Asp Asp Ser
                           105
                                        110
Ala Lys Ala Lys Met Thr Leu Thr Ser Gly Ile Leu Phe Ile Ile Ser
       115
                         120.
                                          125
Gly Ile Cys Ala Ile Ile Gly Val Ser Val Phe Ala Asn Met Leu Val
   130
                   135
                               140
Thr Asn Phe Trp Met Ser Thr Ala Asn Met Tyr Ser Gly Met Gly Gly
145 150
                            155
                                                       160
Met Gly Gly Met Val Gln Thr Val Gln Thr Arg Tyr Thr Phe Gly Ala
           165
                                170
                                                  175
Ala Leu Phe Val Gly Trp Val Ala Gly Gly Leu Thr Leu Ile Gly Gly
        180
                             185
                                               190
Val Met Met Cys Ile Ala Cys Arg Gly Leu Thr Pro Asp Asp Ser Asn
195 200 205
Phe Lys Ala Val Ser Tyr His Ala Ser Gly Gln Asn Val Ala Tyr Arg
  210 215
                               220
Pro Gly Gly Phe Lys Ala Ser Thr Gly Phe Gly Ser Asn Thr Arg Asn
                 230
                                   235
Lys Lys Ile Tyr Asp Gly Gly Ala Arg Thr Glu Asp Asp Glu Gln
                                 250
<210> 706
<211> 255
<212> PRT
<213> Mouse
<400> 706
Met Gly Arg Phe Ala Ala Ala Leu Val Gly Ser Leu Phe Trp Leu Gly
1
               5
                                 10
                                          . 15
Leu Leu Cys Gly Leu Gly Ser Leu Ala Ser Ala Glu Pro Arg Ala
 . 20
                             25
Pro Pro Asn Arg Ile Ala Ile Val Gly Ala Gly Ile Gly Gly Thr Ser
 35
                         40
Ser Ala Tyr Tyr Leu Arg Lys Lys Phe Gly Lys Asp Val Lys Ile Asp 50 55 60
Val Phe Glu Arg Glu Glu Val Gly Gly Arg Leu Ala Thr Leu Lys Val
65 70 75 80
Gln Gly His Asp Tyr Glu Ala Gly Gly Ser Val Ile His Pro Leu Asn
              85
                                 90
                                                95
Leu His Met Lys Arg Phe Val Lys Glu Leu Gly Leu Ser Ser Val Pro
         100
                            105
                                        110
Ala Ser Gly Gly Leu Val Gly Val Tyr Asn Gly Lys Ser Leu Val Phe 115 120 125
                         120
Glu Glu Ser Ser Trp Phe Val Ile Asn Val Ile Lys Leu Val Trp Arg
  130.
                    135
                                      140
Tyr Gly Phe Gln Ser Leu Arg Met His Met Trp Val Glu Asp Leu Leu
               150
                                    155
                                                       160
Asp Lys Phe Met Arg Ile Tyr Arg Tyr Gln Ser His Asp Tyr Ala Phe
              165
                                170
                                                   175
Ser Ser Val Glu Lys Leu Met His Ala Ile Gly Gly Asp Asp Tyr Val
```

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180
                             185
                                                190
Arg Leu Leu Asn Gln Thr Leu Arg Glu Asn Leu Lys Lys Ala Gly Phe
    195
                       200
                                          205
Ser Glu Thr Phe Leu Asn Glu Met Ile Ala Pro Val Met Lys Val Asn
                   215
                                  220
Tyr Gly Gln Ser Thr Asp Ile Asn Ala Phe Val Gly Ala Val Ser Leu
225
       230
                                    235
Thr Ala Ala Asp Ser Asn Leu Trp Ala Val Glu Gly Gly Asn Lys
              245
                                 250 .
<210> 707
<211> 150
<212> PRT
<213> Mouse
<400> 707
Met Ser Trp Trp Arg Asp Asn Phe Trp Ile Ile Leu Ala Met Ser Ile
Ile Phe Ile Ser Leu Val Leu Gly Leu Ile Leu Tyr Cys Val Cys Arg
      20
                            25
Trp Gln Leu Arg Gln Gly Arg Asn Trp Glu Ile Ala Lys Pro Ser Lys
    35
                         40
                                           45
Gln Asp Gly Arg Asp Glu Glu Lys Met Tyr Glu Asn Val Leu Asn Ser
  50
                    55
                                       60
Ser Pro Gly Gln Leu Pro Ala Leu Pro Pro Arg Gly Ser Pro Phe Pro
             70
                                  75
Gly Asp Leu Ala Pro Gln Glu Ala Pro Arg Gln Pro Ser Ala Trp Tyr
             85
                              90
                                                95
Ser Ser Val Lys Lys Val Arg Asn Lys Lys Val Phe Ala Ile Ser Gly
                          105
                                     110
Ser Thr Glu Pro Glu Asn Asp Tyr Asp Asp Val Glu Ile Pro Ala Thr
  115
                        120
                                      125
Thr Glu Thr Gln His Ser Lys Thr Thr Pro Phe Trp Gln Ala Glu Val
Gly Leu His Ser Ser Phe
145
                  150
<210> 708
<211> 114
<212> PRT
<213> Mouse
Met Phe Leu Val Tyr Phe Ser Arg Arg Gly His Cys Ile Asn Tyr Val
              5
                                10
Lys Gly His Ala Asp Ser Leu Ala Pro Trp Cys Cys Gly Val Gly Leu
      20
                            25
Arg Ser Pro Leu Ala Arg Pro Gln His Gly His Val Ser Pro Lys Asp
     35
                      40
His Val Pro Gly Gly His Ala Pro Gly Pro Ser His Lys Trp Leu Cys
                  55
Thr Ala Ala Leu Trp Arg Tyr Leu Glu His Ser Ala Val Thr His Gly
                 70
                                   75 .
Thr Ala Leu Pro Glu Ala His Ala Val Arg Gly Lys His Gly Lys Lys
             85
                               90
                                                  95
Gly Arg Arg Val Val Cys Cys Ser Val Asp Phe Pro Gln Ala Thr Ser
          100
                             105
```

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Leu Phe
<210> 709
<211> 132
<212> PRT
<213> Mouse
<400> 709
Ala His Pro Arg Pro Gly Ala Arg Arg Pro Arg Leu Leu Ala Phe Gln
                                  10
Ala Ser Cys Ala Pro Ala Pro Gly Ser Arg Asp Arg Cys Pro Glu Glu
          20
                              25.
Gly Gly Pro Arg Cys Leu Arg Val Tyr Ala Gly Leu Ile Gly Thr Val
               . 40
      35
Val Thr Pro Asn Tyr Leu Asp Asn Val Ser Ala Arg Val Ala Pro Trp
  50
                   . 55
                                         60
Cys Gly Cys Ala Ala Ser Gly Asn Arg Arg Glu Glu Cys Glu Ala Phe
                 70
                                      75
Arg Lys Leu Phe Thr Arg Asn Pro Cys Leu Asp Gly Ala Ile Gln Ala 85 90 95
              85
                                 90
Phe Asp Ser Leu Gln Pro Ser Val Leu Gln Asp Gln Thr Ala Gly Cys
                           105
                                               110
Cys Phe Pro Arg Val Ser Trp Leu Tyr Ala Leu Thr Ala Leu Ala Leu
      115
                          120
Gln Ala Leu Leu
   130
<210> 710
<211> 255
<212> PRT
<213> Mouse
<400> 710
Met Arg Val Leu Trp Val Leu Gly Leu Cys Cys Val Leu Leu Thr Phe
                                  10
Gly Phe Val Arg Ala Asp Asp Glu Val Asp Val Asp Gly Thr Val Glu
  . 20
                              25
Glu Asp Leu Gly Lys Ser Arg Glu Gly Ser Arg Thr Asp Asp Glu Val
     35
                          40
Val Gln Arg Glu Glu Glu Ala Ile Gln Leu Asp Gly Leu Asn Ala Ser
                     55
                                        60
Gln Ile Arg Glu Leu Arg Glu Lys Ser Glu Lys Phe Ala Phe Gln Ala
                  70
                                    75
Glu Val Asn Arg Met Met Lys Leu Ile Ile Asn Ser Leu Tyr Lys Asn
              85
                                 90
                                                    95
Lys Glu Ile Phe Leu Arg Glu Leu Ile Ser Asn Ala Ser Asp Ala Leu
          100
                            105
                                                110
Asp Lys Ile Arg Leu Ile Ser Leu Thr Asp Glu Asn Ala Leu Ala Gly
       115
                         120
                                             125
Asn Glu Glu Leu Thr Val Lys Ile Lys Cys Asp Lys Glu Lys Asn Leu
  130
                      135
                               . 140
Leu His Val Thr Asp Thr Gly Val Gly Met Thr Arg Glu Glu Leu Val
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245

250

International application No. PCT/NZ01/00099

| A. | CLASSIFICATION OF SUBJECT MATTER | | | | | |
|---|---|--|-----------------------|--|--|--|
| Int. Cl. 7: | C12N 15/12, 15/18, 15/19 | | | | | |
| According to International Patent Classification (IPC) or to both national classification and IPC | | | | | | |
| В. | | | | | | |
| Minimum docu | Minimum documentation searched (classification system followed by classification symbols) | | | | | |
| AS BELOW | | | | | | |
| | Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched AS BELOW. | | | | | |
| | Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) Dgene, Swiss Prot, EMBL, Genebank, : SEQ ID. NOS. 1 - 10. | | | | | |
| C. | DOCUMENTS CONSIDERED TO BE RELEVANT | г | | | | |
| Category* | Citation of document, with indication, where app | propriate, of the relevant passages | Relevant to claim No. | | | |
| P, X | EP 1 067 182 HELIX RESEARCH INSTIT Sequence Id. 487, & GeneBank Accession I | • • | 1 - 3. (SEQ ID NO 1) | | | |
| P, X | EP 1067 182 HELIX RESEARCH INSTITUTE (10 January 2001) See Sequence Id. 219, & GeneBank Accession NumberAX136297. | | 1 - 3. (SEQ ID NO 1) | | | |
| х | EMBL Accession Number AC008119 (9 Oct 12q24.1-116.6-118.9 BAC RPCI11-951I11 | ctober 1999) Homo sapiens | 1 - 3. (SEQ ID NO 1) | | | |
| X | X Further documents are listed in the continuation of Box C X See patent family annex | | | | | |
| * Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) document referring to an oral disclosure, use, exhibition or other means "P" document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention cannot be considered novel or cannot be considered to involve an inventive step when the document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document combined with one or more other such documents, such combination being obvious to a person skilled in the art document member of the same patent family | | | | | | |
| | Date of the actual completion of the international search Date of mailing of the international search report | | | | | |
| Name and mail | ing address of the ISA/AU | Authorized officer | | | | |
| E-man address. pedesipadstrana.gov.ad | | ALISTAIR BESTOW Telephone No: (02) 6283 2450 | : - | | | |

International application No.

PCT/NZ01/00099

| C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT | | | | |
|---|---|---|--|--|
| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. | | |
| Х | US, A, 5 952 486 L. N. BLOKSBERG ET. AL. (14 September 1999) See SEQ ID 53. & GeneBank Accession number AR074144. | 1 - 3. (SEQ ID NO 2) | | |
| x | WO, A, 2000 40752 THE NOTTINGHAM TRENT UNIVERSITY (13 July 2000) See SEQ ID NO. 2. & GeneBank Accession Number AX026540. | 1 - 3. (SEQ ID NO 2) | | |
| X | EMBL Accession Number UCAJ4935 (2 March 1999.) Urechis caupo mRNA for cytoplasmic intermediate filament protein. | 1 - 3. (SEQ ID NO 2) | | |
| X | WO, A, 99 53040 METAGEN GESELLSCHAFT FÜR GENOMFORSCHUNG MBH (21 October 1999) See SEQ ID 31. & GenBank Accession Number AX014842. | 1 - 3. (SEQ ID NO 4) | | |
| P, X | WO, A, 2001 07612 INCYTE GENOMICS, INC. (1 February 2001) See SEQ ID 43 & Genebank Accession Number AX078375. | 1 - 3. (SEQ ID NO 4) | | |
| P, X | WO, A, 2001 10902 CURAGEN CORPORATION (15 February 2001) See SEQ ID 5 & Genebank Accession Number AX084211. | 1 - 3. (SEQ ID NO 5) | | |
| x | EMBL Accession Number AF169677 (29 JANUARY 2000) Homo sapiens leucine-rich repeat transmembrane protein FLRT3 (FLRT3) mRNA, complete cds. | 1 - 3. (SEQ ID NO 5) | | |
| х | EMBL Accession Number RNMOG (20 August 1992) Rattus norvegicus myelin/oligodendrocyte glycoprotein (MOG) gene, complete cds. | 1 - 3. (SEQ ID NO 7) | | |
| A | EMBL Accession Number D50030 (14 April 2000) Homo sapiens gene for hepatocyte growth factor activator, complete cds. | 1 - 3. (SEQ ID NO 8) | | |
| X | WO, A, 99 55865 GENESIS RESEARCH AND DEVELOPMENT CORPORATION LIMITED (4 November 1999) See SEQ ID NOS 1 - 10, 147, 187, 196, 294, 295 and 395. | 1 - 3, 8-17, 27-29 (SEQ ID NOS 1-10, 147, 196, 294, 295, 413-5, 417) | | |
| P, X | WO, A, 2000 69884 GENESIS RESEARCH AND DEVELOPMENT CORPORATION LIMITED (23 November 2000) See SEQ ID NOS 1 - 10, 147, 187, 196, 294, 295 and 395. | 1 - 3, 8-17, 27-29 (SEQ ID NOS 1-10, 147, 196, 294, 295, 413-5, 417) | | |

International application No. PCT/NZ01/00099

| PC1/NZ01/00099 | | | |
|----------------|--|--|--|
| C (Continua | tion) DOCUMENTS CONSIDERED TO BE RELEVANT | | |
| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. | |
| PX | WO, A, 00 63230 HUMAN GENOME SCIENCES, INC. (26 October 2000) See SEQ ID NO 68 and pages 16-29 | 1-3, 8-17, 27- 29 (SEQ ID NOS 196, 413-5, 417 | |
| x | WO, A, 00 29438 MILLENNIUM PHARMACEUTICALS, INC. (25 May 2000) See Figures 1, 3, 5,7 and 8 | 1-3, 8-17, 27- 29 (SEQ ID NOS 196, 413-5, 417 | |
| PX | WO, A, 00 63377 ZYMOGENETICS, INC. (26 October 2000) See SEQ ID NOS 1 and 11 | 1-3 (SEQ ID NO 147, 294) | |
| PX | WO, A, 01 49728 PROTOGENE, INC. (12 July 2001) See SEQ ID NO 59 and Table 1 | 1-3 (SEQ ID NO 147) | |
| PX | WO, A, 00 73448 ZYMOGENETICS, INC. (7 December 2000) Sec SEQ ID NOS 1 and 14 | 1-3 (SEQ ID NO 294) | |
| х | GenPept Accession No. CAB53702 (18 February 2000) Hypothetical Protein Homo sapiens Ottenwaelder B et al | 1-3 (SEQ ID NO 295) | |
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International application No.

PCT/NZ01/00099

| Box I Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet) | | |
|---|--|--|
| This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons: | | |
| 1. Claims Nos: | | |
| because they relate to subject matter not required to be searched by this Authority, namely: | | |
| Claims Nos: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically: | | |
| 3. Claims Nos: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule | | |
| 6.4(a) | | |
| Box II Observations where unity of invention is lacking (Continuation of item 3 of first sheet) | | |
| This International Searching Authority found multiple inventions in this international application, as follows: | | |
| 1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims | | |
| As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee. | | |
| 3. X Sonly some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.: | | |
| 1-3, 8-17 and 27-29 (SEQ ID NOS 1-10, 147, 196, 294, 295, 413-415, 417) | | |
| More than one invention has been claimed. (continued in supplemental box | | |
| 4. No required additional search fees were timely paid by the applicant. | | |
| Remark on Protest The additional search fees were accompanied by the applicant's protest. | | |
| No protest accompanied the payment of additional search fees. | | |

International application No.

PCT/NZ01/00099

Supplemental B x

(To be used when the space in any of Boxes I to VIII is not sufficient)

Continuation of Box No: II

Rule 13.1 of the PCT states the principle that an International Application should relate to only one invention or, if there is more than one invention, that the inclusion of those inventions in one International Application is only permitted if all inventions are so linked to form a single general inventive concept. Rule 13.2 of the PCT defines the method for determining whether the requirement of unity of invention is satisfied in respect of a group of inventions claimed in the International application. Unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding "special technical features." The expression "special technical features" is defined in Rule 13.2 as meaning those technical features that define a contribution which each of the inventions, considered as a whole, makes over the prior art. The determination is made on the contents of the claims as interpreted in the light of the description and drawings (if any).

There is no special technical feature which is common to all 725 sequences disclosed in the specification. It is well known in the art that for a given cell type, the cell will express a great many sequences, each having a different function from the others. That they are sourced from skin, cells is not a special technical feature. For applications claiming nucleotides and peptides, there are two features which are to be considered for the purposes of determining the number of inventions in a specification.

1) If the polynucleotide has a corresponding peptide, then the two sequences may have a common special technical feature because the nucleotide encodes the peptide. Therefore they are regarded as a single invention.

In the present case, the specification does not disclose a complete concordance between the polynucleotides and corresponding polypeptides, other than those disclosed in Table 2. While Table 2 purports to provide a concordance between nucleotides and peptides for which they code, this is incomplete, as the majority of sequences are not referred to on this table. Therefore the ISA is unable to confidently determine the number of inventions, on the basis of a concordance between the polynucleotides and the peptides.

2) A group of two or more nucleotides, or two or more peptides, which share a significant structural element. A "significant structural element" is the structural element that defines the specific biological activity of an amino acid sequence or a nucleotide sequence or its encoded polypeptide and is disclosed as the feature that defines the contribution which each of the inventions, considered as a whole, makes over the prior art. If each of the inventions shares the same significant structural element, then it provides the special technical feature which is required to establish unity of invention.

In the present case, genes and their expressed proteins from skin cells have been sequenced. The applicant has provided no evidence that the nucleotide sequences of the present application, and the peptides they express, all form a group of protein types sharing a significant structural element. On the contrary, the putative peptides derived from the nucleotide sequences of the application have a wide range of functions based on their similarity to known proteins. (see Table 2) At best, it appears from Table 2 that there may be 76 distinct protein types which share a common function, and therefore may share a common significant structural element. However, most of the polynucleotides and peptides which do not appear on Table 2, have not have been identified in terms of their function, much less, whether any of them have a shared significant structural element. Therefore, the ISA is unable to confidently determine the number of inventions, on the basis of a shared significant structural element. Thus, at this stage, in the absence of a complete polynucleotide peptide concordance, or the definition of a special technical feature which is common to two or more sequences, this ISA considers that that there are 72 groupings of sequences, which encompass the 725 sequences.

While the ISA is unable to determine the precise number of inventions in this application it is prepared, as a service, to search a first group of ten sequences for a single search fee. This offer is provided purely as a service to the applicant and should not be taken as having any bearing on the ISA's assessment of the number of inventions claimed in these 10 sequences. The ISA also agrees to search the two further inventions specified by the applicant in their letter of 30 August 2001, for two additional search fees. As such, the ISA has searched SEQ ID NOS 1-10, 147, 196, 294, 295, 413-5 and 417.